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PULMONARY HYPERTENSION IN HEART DISEASE*

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THE pulmonary circulation is of paramount importance in failure of the heart. The presence of dyspnea, orthopnea and hemoptysis and a diminution in vital capacity imply a profound change in the blood vessels of the lungs. Unfortunately, the pulmonary circulation, being effectively enclosed within the thorax, has proved inaccessible to quantitative measurements until recently.

In spite of this lack of quantitative evidence, clinicians and pathologists have been able to deduce from indirect evidence the course of events in the pulmonary circulation in heart disease. The importance of hypertension of the pulmonary circulation in the natural history of mitral stenosis has been appreciated for many years. Many of the classic signs of this type of cardiac disease have been thought to be indications of increased pressure in the pulmonary artery. Examples are the accentuated second sound in the pulmonic area, the Graham-Steell murmur, the dilatation of the pulmonary artery and right ventricle and the electrocardiographic pattern of right-ventricle hypertrophy. The pathologist has reinforced the clinician's opinion of the importance of pulmonary hypertension by describing marked hypertrophy of the right ventricle and sclerotic changes in the large and small pulmonary arteries.

In failure of the left ventricle due to systemic hypertension or disease of the aortic valve the clinical and pathological pictures differ from those in mitral stenosis. The symptoms, at least during the early stages, tend to be periodic and are characterized by paroxysms of severe dyspnea, at times accompanied by pulmonary edema. Weiss and Robb[1] have described the mechanism of these attacks as follows:

> The disturbed balance between the coronary blood flow and the metabolic requirement of the muscle of the left ventricle, as compared with the right ventricle, is the primary factor in the pathogenesis of cardiac asthma. As a result, the reserve functional capacity of the left ventricle becomes disproportionately impaired, and later, according to the observations presented, there follows a back pressure effect within the pulmonary circuit, usually without failure of the peripheral circulation. In this engorged state of pulmonary circulation the reserve pulmonary vessels are taken up by blood, and pulmonary vascular hypertension of moderate to severe degree develops.

Between attacks the patients may be relatively comfortable except for exertional dyspnea; the intensity of the pulmonic second sound, which is accentuated during the attacks, again becomes less than that of the aortic second sound. One is therefore led to the conclusion that pulmonary hypertension in such a patient is severe during the attacks of cardiac asthma and mild or absent at other times. The fact that pronounced hypertrophy of the right side of the heart and pulmonary arteriosclerosis are rare in diseases involving primarily the left ventricle also speaks against the presence of sustained pulmonary hypertension.

The development of catheterization of the right side of the heart now permits pressure measurements in the pulmonary artery in human beings.[2] By the use of this technic the normal pressure in the pulmonary artery has been found to be about 20 systolic, 9 diastolic,[3] the normal mean pressure in the artery being around 15.[4] Although measurement of pressures in the pulmonary veins and in the left auricle in normal human beings is not yet possible, some information has been obtained from the study of patients with uncomplicated defects of the interauricular septum. By passing the catheter through the defect one can measure the pressure in the left auricle and pulmonary vein, and they have been found to be 4 and 6 respectively.[5] It is obvious that the pressure gradient, or decline in pressure, from pulmonary artery to pulmonary vein is quite small (probably no more than 10). It

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also follows that an increase in the pressure in the pulmonary vein must be associated with a corresponding increase in that in the pulmonary artery if the pulmonary blood flow is to be maintained. Actual measurements in dogs have shown such an increase under experimental conditions.[6, 7] The situation in the systemic circulation stands in sharp contrast, since the gradient of pressure between artery and vein is very large and changes in venous pressure affect arterial pressure little if at all.

The application of the technic of catheterization of the right side of the heart, not only to the study of normal pulmonary hemodynamics but also to the abnormal situations prevailing in some types of cardiac disease, is already well advanced. Numerous studies have been made in cases of congenital heart disease.[8] In patients with mitral stenosis, high systolic pressures have been recorded in the right ventricle.[9] The present study undertakes to correlate the pulmonary-artery pressure with the physical status in a group of patients with disease of the mitral valve. The same relations have also been examined in a second group of patients suffering from chronic failure of the left ventricle due to systemic hypertension or to disease of the aortic valve. The technics used in this study have been described previously.[5]

Mitral Disease

The pulmonary-artery pressure was measured in 31 patients with mitral disease. The predominant lesion in 30 of the patients was mitral stenosis, and in the 1 remaining it was pure mitral insufficiency. In 10 patients there was an associated aortic insufficiency, but in only 3 was this lesion of sufficient severity to produce changes in the pulse pressure; in none was there evidence of significant enlargement of the left ventricle. Auricular fibrillation was present in 12 and systemic arterial hypertension in 2 cases at the time of the study. Only 1 patient was female. The average age for the group was thirty-eight years.

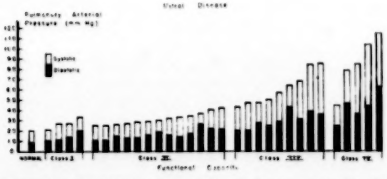

Figure 1. *Graphic Representation of Pressures in the Pulmonary Arteries of 31 Patients with Mitral Disease Grouped According to Functional Capacity (New York Heart Association Classification).*

The values obtained for the individual patients, grouped according to functional classification, are shown in Figure 1. It is immediately apparent that there is a rough linear correlation between the pulmonary-artery pressure and the functional capacity as expressed by the criteria of the New York Heart Association.[10] In other words, patients who were asymptomatic or only slightly incapacitated by exertional dyspnea (Classes I and II) showed normal or slightly elevated pressures; those who were partly or completely incapacitated by exertional dyspnea (Classes III and IV) usually showed markedly elevated values. More precisely, the average values in a group of 12 normal subjects were 20 systolic, 9 diastolic[5]; in the 17 patients with mitral-valve disease (Classes I and II) the corresponding values were 30 systolic, 16 diastolic, and in 14 patients with mitral disease (Classes III and IV) they were 69 systolic, 34 diastolic. The mean figures in the three groups for the diastolic pressure in the right ventricle were 2.9, 3.6 and 6.3, respectively. High pressures in the pulmonary artery were usually associated with a low pulmonary blood flow. The cardiac output was determined in 15 of the patients in Classes I and II, and in 13 of the patients in Classes III and IV. The mean cardiac index for the former was 3.2 liters per minute, — a value quantitatively similar to that obtained in normal persons,[11] — and that in the latter was 2.3 liters per minute, or about 25 per cent less than the normal figure. Five patients in the latter group died three to eleven months after the study. The average cardiac index in these 5 patients was 2.1 liters per minute, and the average pulmonary-artery pressure was 93 systolic, 45 diastolic.

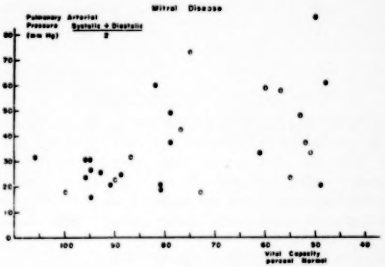

Figure 2. *Correlation between Pressure in the Pulmonary Artery and Reduction in Vital Capacity in Mitral Stenosis ($r = 0.4898$, $p. < 0.01$).*

Open circles represent patients with auricular fibrillation; closed circles represent those with normal sinus rhythm.

The correlation between the pulmonary-artery pressure and the vital capacity in mitral stenosis (Fig. 2) was less striking than we had expected, although patients with moderate to marked pulmonary hypertension all had a decrease in the vital capacity. Certain patients with severe reduction in vital capacity, however, did not show a marked elevation in pulmonary-artery pressure.

None of the patients had orthopnea at the time cardiac catheterization studies were performed, but the majority of those with marked pulmonary hypertension had noted this symptom prior to admission to the hospital. Frank hemoptysis occurred in 5 patients, all of whom had moderate to marked pulmonary hypertension. The average pulmonary-artery pressure for this group was 61 systolic, 33 diastolic. Seven patients had failure of the right ventricle manifested by peripheral edema, hepatomegaly and an elevated venous pressure at some time during the course of their disease. All 7 had severe pulmonary hypertension, the average pulmonary-artery pressure for the group being 82 systolic, 41 diastolic. A distinctly accentuated pulmonic second sound was invariably associated with the presence of pulmonary hypertension and was absent in patients whose pulmonary-artery pressures were normal. A Graham-Steell murmur was diagnosed clinically in 4 patients, all of whom had severe pulmonary hypertension by direct measurement. Two of the 4 patients subsequently died, and at autopsy no evidence of disease of the aortic or pulmonic valves could be found. The pressures in these 2 cases were 84 systolic, 39 diastolic, and 114 systolic, 62 diastolic, respectively.

The electrocardiographic and roentgenologic changes also reflected to some extent the degree of pulmonary hypertension. Eleven of the 31 patients showed right-axis deviation (+ 90° or more). The pulmonary-artery pressures in this group varied from 33 systolic, 14 diastolic, to 114 systolic, 62 diastolic, the mean figure being 69 systolic, 35 diastolic. The roentgenologic examination of the heart in patients with normal pressures or mild pulmonary hypertension revealed either a normal cardiac silhouette or straightening of the left border of the heart with slight enlargement of the left auricle. Severe pulmonary hypertension presented a characteristic roentgenologic picture, which consisted of enlargement of the pulmonary arteries, moderate to marked enlargement of the left auricle, enlargement of the right ventricle and a reticular or finely mottled appearance of the lungs (Fig. 3). There was no exact correlation between the size of the left auricle and the degree of pulmonary hypertension. For example, the patient with the most severe degree of pulmonary hypertension (114 systolic, 62 diastolic) had only moderate enlargement of the left auricle roentgenologically and at autopsy.

Failure of the Left Ventricle

The pulmonary-artery pressure was measured in 23 men with failure of the left ventricle. All had exertional dyspnea for a period varying from six years to one month prior to entry to the hospital, and all had suffered one or more episodes of paroxysmal nocturnal dyspnea. Moderate to marked enlargement of the left ventricle was present in all cases. The etiology of the heart disease was systemic arterial hypertension in 11 patients, syphilitic aortic insufficiency in 2, rheumatic aortic insufficiency in 5, aortic stenosis in 1 and aortic stenosis and insufficiency in 4. The average age for the group was fifty-two years.

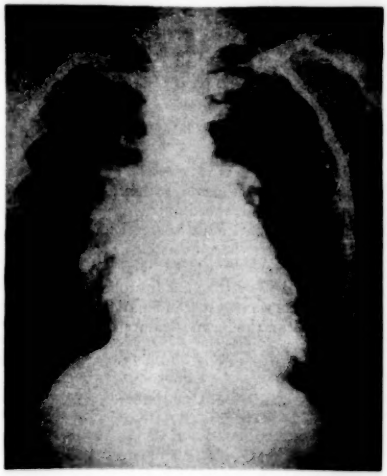

Figure 3. *Teleroentgenogram in a Patient with Advanced Mitral Stenosis, Severe Pulmonary Hypertension and a Graham-Steell Murmur.*

The pulmonary-artery pressure was 84 systolic, 39 diastolic. (Note the straightening of the left border of the heart, the dilatation of the pulmonary arteries and the absence of pulmonary edema.)

The values for the pulmonary-artery pressure in the individual cases are presented in Figure 4. Some increase was present in all but 3 patients, the average pressures for the group being 38 systolic, 18 diastolic (normal 20 systolic, 9 diastolic). The average diastolic pressure in the right ventricle was 4.5 (normal 2.9). The pulmonary blood flow in this group of patients was significantly diminished, but to a lesser degree than in advanced mitral

disease. The mean cardiac index in the 20 patients in which it was determined was 2.8 liters per minute. There was no correlation between the pulmonary-artery pressure and the reduction in vital capacity (Fig. 5).

Although dyspnea — and at times orthopnea — was severe in most of the patients with failure of

FIGURE 4. *Graphic Representation of the Pulmonary-Artery Pressures in 23 Patients with Left-Ventricle Failure.*

the left ventricle, the elevation in pulmonary-artery pressure was never as marked as that seen in patients with advanced mitral disease. Orthopnea developed in 2 patients while catheterization of the right side of the heart was being performed; the pulmonary-artery pressures were 39 systolic, 12 diastolic, and 57 systolic, 23 diastolic. Failure of the right ventricle was present in 3 patients on admission to the hospital; the mean pressure for this group was

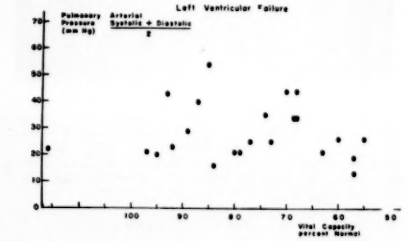

FIGURE 5. *Lack of Correlation between the Pulmonary-Artery Pressures and the Reduction in Vital Capacity in Patients with Failure of the Left Ventricle ($r = 0.0399$).*

49 systolic, 23 diastolic. Nine of the patients died one to twelve months after the study. Death was due to pulmonary edema in 6 cases, uremia in 2 cases and massive cerebral hemorrhage in 1 case. The average pulmonary-artery pressure in the 6 patients who later died with pulmonary edema was 36 systolic, 24 diastolic.

DISCUSSION

The level of the pressure in the pulmonary artery is dependent upon three hemodynamic factors: the pressure in the pulmonary vein, the resistance to flow offered by the pulmonary vascular bed and the output of the heart. A complete appraisal, in physiologic terms, of the mechanism of pulmonary hypertension in heart disease must take into account these three factors, which may operate independently or simultaneously to raise the pulmonary-artery pressure. At the outset, an increase in the cardiac output may be disregarded as a factor of importance in the maintenance of a sustained elevation of the pressure since in mitral stenosis and failure of the left ventricle the blood flow through the lungs is either normal or decreased. On the other hand an elevation of pressure in the pulmonary vein, with a consequent elevation of pressure in the pulmonary capillaries and pulmonary artery, has, for many years, been invoked to explain pulmonary hypertension in both mitral stenosis and left-ventricle failure. Although this view ignores the possibility of an increase in pulmonary vascular resistance in the pathogenesis of pulmonary hypertension it has considerable merit. In mitral stenosis, for example, contracture of the mitral valve offers a definite mechanical obstruction to the flow of blood at the venous end of the pulmonary circuit. The continuing output of the right ventricle, whether it is normal or decreased, meets this obstruction, and the pressure in the left auricle and pulmonary veins rises. This creates a gradient of pressure between the left auricle and left ventricle, thereby permitting blood to flow through the constricted mitral orifice. An etiologically different, but dynamically similar, mechanism obtains in failure of the left ventricle. When the left myocardium becomes insufficient, an increased filling pressure is required if the output of the left ventricle is to be maintained. In effect, myocardial failure constitutes a resistance to flow into the left ventricle. The continuing output of the right ventricle raises the pressure in the left auricle and pulmonary vein until a pressure gradient between the left auricle and left ventricle is established and the resistance is overcome. In either situation, mechanical obstruction or myocardial failure, the pressures in the pulmonary arteries and capillaries have been assumed to rise proportionately to the elevated pressure in the pulmonary vein. The implication of this assumption is that the pressure gradient between the pulmonary artery and vein remains unaltered.

The normal pressure gradient across the pulmonary circuit, as noted above, is small and to be accurately determined requires the simultaneous measurement of the pressures in the pulmonary artery and vein. The inaccessibility of the left auricle prohibits this measurement except in occa-

sional cases of defect of the interauricular septum or during operations on the heart. By the use of the catheter technic in dogs with a closed thorax, the pressures in the pulmonary arteries and veins can be measured simultaneously, and Haddy et al.[6, 7] have recently shown that acute elevations in the pressure of the pulmonary vein are accompanied by corresponding elevations in those of the pulmonary artery. The gradient of pressure between the pulmonary artery and vein remained the same, and pulmonary edema occurred regularly when the pressure in the pulmonary vein rose above 20. These experiments give considerable support to the classic theory of pulmonary hypertension outlined above, and add credence to the probable mechanism of acute cardiac asthma proposed by Weiss and Robb.[1]

There remains, however, the problem of whether or not established pulmonary hypertension in heart disease is due entirely to chronic elevation of pressure in the pulmonary vein or in part to an increased vascular resistance with an increased gradient of pressure between the pulmonary artery and vein. The pulmonary-artery hypertension that is not infrequently found in chronic pulmonary emphysema is clearly attributable to increased vascular resistance.[12] The severe pulmonary hypertension that has been observed in certain cases of congenital heart lesions with a left-to-right shunt[8, 13-15] and in Eisenmenger's complex[16] is undoubtedly on the same basis. Although direct measurement of the pulmonary-pressure gradient in the common types of heart disease is not yet feasible, there is reason to believe that a portion of the pulmonary hypertension in mitral stenosis is the result of an increased vascular resistance, particularly when the level of pressure approaches that in the systemic circuit.

Clinical evidence supporting this view is present in the observations forming the basis of this report. If the elevation in the pressure of the pulmonary arteries in mitral stenosis is a reflection of a corresponding elevation in that of the pulmonary veins and capillaries, one would expect severe pulmonary hypertension to be accompanied by clinical and roentgenologic evidence of marked pulmonary congestion and edema. Several of the patients with mitral stenosis and severe pulmonary hypertension had orthopnea, numerous pulmonary rales and roentgenologic evidence of pulmonary edema at some time during the course of their disease. At the time the pressures in the pulmonary arteries were measured, all patients were able to lie flat with complete comfort. Auscultation of the lungs revealed no rales, and roentgenograms of the chest showed no evidence of massive pulmonary edema. Moreover, measurement of pulmonary blood volume by a dye-injection technic in 10 of the patients in this group revealed no significant increase in the volume of blood in the lungs.[17] Thus, in mitral stenosis, the arterial pressure in the lungs can approach the level of the systemic arteries in the absence of dyspnea at rest and in the absence of signs of frank pulmonary edema. This dissociation, therefore, between pulmonary hypertension on the one hand and pulmonary congestion and edema on the other suggests an increase in vascular resistance.

Characteristic anatomic lesions in the lungs have been described at autopsy in patients dying of mitral stenosis.[18-20] The alveolar septums are thickened, owing to the presence of edema and increased amounts of fibrous tissue. In advanced stages of this process the alveoli may be lined with cuboidal epithelium; sclerotic changes in the walls of the pulmonary arterioles often occur and occasionally become so pronounced that they resemble the vascular lesions of the kidney in malignant hypertension. Under these circumstances the pulmonary capillaries can probably sustain high pressures without allowing massive intra-alveolar edema to occur. It is also likely that the pulmonary arterioles offer an increased resistance to blood flow so that the high pressure in the pulmonary artery is not directly transmitted to the capillaries. Larrabee, Parker and Edwards[19] have recently offered pathological evidence in favor of this view.

Whatever the mechanism of pulmonary hypertension in mitral stenosis may be, it has been established that sustained severe pulmonary hypertension is an almost universal feature of the symptomatic phase of the disease. This fact is basic for an understanding of the clinical manifestations of mitral stenosis; in essence, the natural history of the disease is explained by alterations in the pulmonary circulation with secondary involvement of the right ventricle. The close correlation between the level of the pressure in the pulmonary artery and the symptomatology enables the clinician to evaluate more accurately the disability and prognosis presented by the individual patient.

The findings in this study confirm the classic notion that many of the signs of mitral disease are actually signs of sustained pulmonary-artery hypertension. An accentuated pulmonic second sound, for example, was found only in the presence of pulmonary hypertension, and should be considered a sign of pulmonary hypertension and not a sign of mitral stenosis per se. The murmur of functional pulmonic insufficiency was noted only when the pulmonary hypertension was extreme, thus vindicating the original description, in 1888, of Graham Steell,[21] whose treatise was entitled, "The Murmur of High-Pressure in the Pulmonary Artery." The roentgenologic evidence of enlargement of the right side of the heart and dilatation of the pulmonary artery was characteristic of pulmonary hypertension; so also were the electrocardiographic patterns of right-axis deviation and right-ventricle strain. Failure of the right ventricle was always associated with severe pulmonary hypertension, which apparently had existed for a long time. It seems inescapable, therefore, that the simple mechanical

strain of prolonged pulmonary hypertension, although well tolerated by a myocardium that is not intrinsically diseased, is the principal cause of failure of the right ventricle in mitral stenosis.

The elevation of pulmonary-artery pressure was much less marked in the patients with failure of the left ventricle than in those with mitral stenosis. Since the pressures reported here were measured at a time when the patients were fairly comfortable it is quite likely that the pulmonary pressures would be higher if measured during an attack of cardiac asthma. The lack of correlation between the degree of pulmonary hypertension and the reduction in vital capacity in failure of the left ventricle was unexpected. The reduction in vital capacity in this type of failure has been shown to be accompanied by decreased pulmonary distensibility, which in turn has been attributed to pulmonary congestion and edema.[22] Since the pressure in the pulmonary artery had no apparent relation to the reduction in vital capacity, changes in vascular pressure cannot be directly incriminated in the reduction of this function. Varying degrees of interstitial pulmonary edema could well account for this finding in failure of the left ventricle particularly in patients with a low vital capacity and only slight elevation of the pressure in the pulmonary artery (Fig. 5).

Failure of the right ventricle in aortic-valve and hypertensive heart disease was not related to the duration or severity of pulmonary hypertension, in contrast to the situation found in mitral stenosis. This is in accord with well known clinical observations. White[23] has stated that failure of the right ventricle may occur almost simultaneously with that of the left ventricle or at times failure of the left ventricle may exist alone for years without failure of the right. Moreover, the right ventricle is seldom greatly hypertrophied in most patients dying of aortic-valve and hypertensive heart disease. These considerations implicate intrinsic myocardial disease in addition to a mild pulmonary hypertension in failure of the right ventricle that is consequent to failure of the left.

Summary

The values for the pulmonary-artery pressure in 31 patients with mitral disease and 23 patients with failure of the left ventricle are reported in a study correlating the degree of pulmonary hypertension with clinical manifestations. In patients with mitral stenosis the degree of pulmonary hypertension was closely related to the symptomatology and disability from exertional dyspnea. Sustained severe pulmonary hypertension was a constant feature of the advanced stages of mitral disease and accounted for many of the classic physical findings, as well as the development of failure of the right ventricle. Evidence is presented that suggests that severe pulmonary arterial hypertension in mitral stenosis is not due entirely to an elevation of pressure in the left auricle but is due, in part, to an increase in vascular resistance of the lung.

Pulmonary-artery hypertension, on the other hand, was less marked in failure of the left ventricle and not nearly so constant a feature of the disease. There was no correlation between the reduction in vital capacity and the pressure in the pulmonary artery. This indicates that the reduction in vital capacity is related to pulmonary edema rather than to pressure changes in the vascular system of the lung.

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VERATRUM VIRIDE AND ESSENTIAL HYPERTENSION*

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VERATRUM viride, the American false hellebore, has been used intermittently for over a hundred years in the treatment of fever, tachycardia and disturbances of the circulation. However, in modern times it has been generally discredited for clinical use, except by a rare pharmacologist[1] and an occasional obstetrician who has continued to advocate it for the relief of acute toxemias of pregnancy.[2-4] Recently, it has been tried clinically in cases of essential hypertension,[5-7] with results favorable enough to stimulate physiologic studies of its hemodynamic effects in man[8, 9] and renewed pharmacologic attempts at isolation of its clinically active principles.[10, 11] This paper is a summary of the present status of the work on *V. viride* in relation to essential hypertension.

PREPARATIONS

V. viride, which is to be distinguished from the European *V. album*, heretofore has been clinically available as a tincture, an aqueous extract or simply as a powder of the dried rhizomes and roots. Unfortunately, different batches of the crude drug may vary widely in hypotensive activity. Furthermore, except when special precautions are taken, the drug may lose potency. Therefore, lack of uniformity of action has been a clinical complaint about the ordinary preparations. This feature, although objectionable enough in the short-term treatment of an acute hypertensive state such as eclampsia, is even more undesirable in the long-term therapy of a chronic disease like essential hypertension. To meet these objections, therefore, efforts have been made, first, to furnish preparations that are biologically standardized, second, to produce stable, chemically purified extracts and, third, to isolate the active principles of the drug, presumably alkaloids, in pure form. An additional aim, of course, in purifying the drug and in isolating its active principles was to eliminate so far as possible any unpleasant side effects that might be due to contaminants or nonhypotensive constituents of the crude preparations.

Among the currently available preparations of *V. viride*, one is a partially soluble aqueous extract, Veratrone, suitable for intramuscular injection; one is a stabilized powder of the dried root, Vertavis, biologically standardized and put up in tablet form for oral administration; and two are purified alkaloidal extracts, Veriloid,‡ which is biologically standardized, and preparation V-056-11,‡ both in tablet form for oral use. The action of these different preparations is similar and is discussed below.

In the past, biologic standardization of Veratrum preparations was attempted with a number of different species of small animals including daphnia, frogs, mice, rats, pigeons, guinea pigs and rabbits. Thus, the dose of the preparation Vertavis sufficient to produce systolic arrest of the daphnia heart has been called the Craw unit, after the worker who developed this method of assay.[12] The dose of preparations necessary to cause toxic reactions or death in various other small animals has also been used as a measure of their activity. It is of interest that early in such bioassay work it was discovered that many small animals, particularly mice, apparently dead from overdoses of the drug, subsequently recovered completely with no apparent ill effects. This observation, and also the desirability of assaying the drug in terms of the clinically desired vasodepressor action, led Maison and Stutzman[13] recently to try larger animals. They employed physiologic standards such as the hypotensive and bradycrotic effects of the drug, rather than its toxic or lethal actions, in establishing the potency of a preparation.

Of all animals tried so far, the dog appears to be the most suitable for the bioassay of *V. viride*. More comparable in size and in cardiovascular reactions to man, it also is susceptible to, and may be studied during, the emetic effect of *V. viride*, which is of considerable clinical importance. However, like other animals it may show marked variations in susceptibility to the drug. This not only necessitates the use of several animals for any one bioassay but also limits the accuracy with which the assay can easily be made. Nevertheless, repeated tests of many different preparations of *V. viride* in the dog have both verified the reproducibility of the bioassay method in this animal and, importantly, shown the validity of the results as applied to human beings. Thus, preparations inactive in the dog have proved to be inactive also in man, and various active preparations have had relatively the same potency in dog and man.

Veriloid, recently described by Stutzman, Maison and Kusserow,[10] is a mixture of alkaloids, among which are highly potent and clinically active principles of *V. viride*. This fact was established by

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‡Still in the status of experimental drugs and not yet commercially available.

bioassay in the dog of all fractions of the crude drug obtained in the process of extracting Veriloid, and of Veriloid itself, as compared with the aliquots of the crude drug from which they were derived. In addition, similar studies of compounds obtained by further fractionation of Veriloid have revealed none of the previously described potent alkaloids of Veratrum. The latest evidence obtained by these workers indicates that the active principles of Veriloid are amorphous compounds, probably ester alkaloids.

Within the past decade certain purified crystalline alkaloids of *V. viride* have been prepared chemically by Jacobs and Craig[14] and studied pharmacologically in animals by Krayer and his co-workers.[15] However, these represented only a small fraction of the alkaloidal material in the crude drug. Moreover, they were not compared in activity with the aliquots of crude root from which they were obtained, nor were the impure residual fractions produced in the separation process subjected to further fractionation or study. Thus, there was no evidence that the clinically hypotensive activity of crude *V. viride* was due to the effects of any of the crystalline alkaloids obtained. Finally, none of the crystalline compounds derived from *V. viride* were tried in the treatment of hypertensive patients, although Protoveratrine, a crystalline derivative of *V. album*, was recently given acutely by parenteral injection to hypertensive subjects,[16] with hypotensive effects similar to those of preparations of *V. viride* so administered.

During the past three years, Fried, White and Wintersteiner,[17] working in co-operation with Freis, Stanton and Moister,[11] have repeated the process of fractionation of the crude drug and have succeeded in isolating and identifying two hitherto undescribed, chemically pure, amorphous alkaloids as clinically active principles of *V. viride*.* To allow no chance that an erroneous choice of an assay animal would produce a false impression of the clinical activity of a preparation, all the fractions and derivatives of the process, beginning with the crude drug and including the tars, residues and amorphous compounds, as well as the crystalline alkaloids, were bioassayed *in man*, against aliquots of the crude drug from which they were obtained. This involved over 400 tests on 102 different fractions, including preparation V-056-11, a highly purified extract that contains the two active amorphous alkaloids. As a result of this extensive investigation, it now appears that among the chief clinically active principles of crude *V. viride* there are two pure amorphous compounds that may be prepared as crystalline derivatives without loss of potency. Preliminary clinical studies of the effects of these two alkaloids indicate that their action in every way is similar to that of crude *V. viride*. Further pharmacologic and physiologic studies in man are now in progress in this laboratory.

*These have not yet been made available in quantities sufficient for trial in prolonged therapy.

Effects of *Veratrum Viride* in Hypertensive Human Beings

The hypotensive effects of *V. viride*, whether crude root, purified extract or pure alkaloid, are apparently similar in normal animals, normal human beings and hypertensive patients. Generally vasodilator, these effects may be mediated through the central nervous system. Krayer and his co-workers,[18] in their studies of crystalline alkaloids, found that the action was largely reflex, involving peripheral sensory endings of the vagus nerve. In the action of Veriloid, it has been shown that the participation of the sensory vagus is not important.[10] Bradycardia, a motor vagus effect, is a usual though not a necessary component of the vasodepressor action of the drug, since it may be abolished by atropinization in man or vagectomy in the dog without greatly affecting the hypotension. Salivation, nausea and vomiting are the most frequent of the unpleasant side effects, and circulatory collapse the most alarming — though usually an innocuous — evidence of overdosage of the drug. As antidotes for these reactions, atropine (0.5 to 1.0 mg.) or ephedrine (30 to 45 mg.) or both have been given intramuscularly.

As for its specific hemodynamic effects in man, studies in this laboratory[8, 9] have shown that during the hypotensive response to *V. viride* cardiac output does not decrease but, on the contrary, may increase, particularly in patients with reduced cardiac outputs due to hypertensive cardiac failure. In no sense sympatholytic, the drug leaves the vasomotor reflexes and postural adaptations intact. Although renal blood flow initially may decrease with the first sizable fall in arterial pressure after administration of the drug, it returns to control values when the pressure becomes stabilized at the lower levels. Blood flow through the portal circuit of the liver behaves in a similar fashion, decreasing early but returning to control values later during the stable phase of the hypotensive reaction. Likewise, blood flow in the limbs is essentially unchanged during the hypotensive response to *V. viride*. Although blood flow through the brain has not yet been measured, clinical impressions of the patient's sensorium and ophthalmoscopic observations of the eye grounds suggest that these areas receive adequate circulation during the hypotension.

Therapeutic Use of *Veratrum Viride* in Hypertension

It must be pointed out that the long-term treatment of a chronic disease is a different matter from short-term therapy of an acute disturbance, or of a crisis in a chronic disease. This is particularly true in essential hypertension, which, contrary to general opinion, is usually more than normally

susceptible to the immediate effects of hypotensive drugs and procedures. Thus, hypertensive patients have notoriously unstable arterial pressures under many conditions, including general or spinal anesthesia and pyrogenic reactions. However, neither of these procedures can conceivably be termed ideal or physiologic for the long-term therapy of essential hypertension, although the first has been used briefly and the second repeatedly over prolonged periods in certain severe forms of the disease.[18] Similarly, acute reactions to single doses of any drug, including *V. viride* (which in hypertensive crises may be very striking), no matter how impressive, are of little importance in indicating the usefulness of the drug for continuous treatment. For not only do all the considerations involved in the long-continued use of any medication arise, but also the problem is enormously complicated by the tendency of hypertensive disease itself to vary in severity and to respond better to the initial than to the continued use of the same therapy. Finally, as others have also pointed out, only statistical analysis of five, ten or twenty years' results of closely studied, carefully graded cases can truly answer the question of the practical value of any treatment in this disease. In this connection it should be emphasized that, to be practicable for continuous treatment of hypertension, a drug should be effective by mouth, sufficiently lasting in action so as not to require too frequent dosage, free of dangerous or objectionable side effects and available in amounts and at costs suitable for long-term use by the average patient.

Although these facts are realized, it has been interesting to observe the effects of *V. viride* in two small groups of patients treated (with Vertavis or Veriloid) in this clinic for a number of months. It was soon obvious that the drugs were at best palliative, not curative. Furthermore, the hypotensive effects during continuous treatment were considerably less than those on initial trial. Largely, this appeared to be because of the necessity of repeated adjustment of dosage so that nausea or vomiting did not occur, but it also may have been due in part to the operation of other humoral or neurogenic mechanisms set in motion after chronic administration of the drug.

Nevertheless, as judged by the average arterial pressures, 80 per cent of the patients treated were improved. Thus, on Vertavis[6] 11 per cent of 34 patients followed for one to thirteen months had a lowering of 50 mm. or more, and 70 per cent a lowering of 20 or more in average systolic pressure, and 14 per cent had a decrease of 30 or more, and 41 per cent a decrease of 20 or more in average diastolic pressure. Similarly, in 20 patients followed for six to twenty weeks on Veriloid[7] the average systolic pressure showed a reduction of 50 mm. or more in 30 per cent and 20 or more in 70 per cent, and the diastolic a lowering of 30 or more in 30 per cent and 20 or more in 70 per cent. In both groups, only rarely was the arterial pressure restored to normal, and in these cases the pressure initially had not been excessively high. Rather, the characteristic effect of the drug was to moderate, not to eliminate, the hypertension.

Associated symptoms and signs of hypertension in general have been favorably affected or at least have remained unchanged in patients whose arterial pressures have been lowered during continuous treatment with *V. viride*. Similar observations have been reported after a number of other measures, which have successfully reduced the arterial pressure in hypertensive patients for prolonged periods. Thus, in favorable cases, cardiac enlargement, with or without frank congestive failure, has decreased, competence has increased, and electrocardiographic abnormalities have improved after Veratrum therapy. Retinopathy has decreased, in some cases in a startling fashion. Renal function, except in certain cases of chronic nitrogen retention that progressed during therapy, has remained adequate. Only 4 patients have had signs of cerebrovascular accidents while on the drug, and in only 1 of these was it possibly due to a hypotensive reaction to the drug.

On continued administration there have been no evidences of development of tolerance or idiosyncrasy to the drug. Unfortunately, on long-term treatment almost all patients have experienced more or less nausea and vomiting, and a few have had collapse reactions similar in every way to those following acute overdosage. In part, this undoubtedly is due to the critical dosage requirements of the drug, which are described below. In part, it seems also to be due to the fact that patients on continuous oral treatment, especially with Veriloid, apparently become more reactive to the same doses of the drug, and require a reduction of dosage after several weeks of therapy, to avoid nausea and vomiting or excessive hypotensive reactions, or both. Finally, there is a question whether some of the nausea and vomiting may be a central-nervous-system effect indissolubly associated with acute systemic hypotension, since similar symptoms occur from comparable hypotensive responses whether to spinal anesthesia, pyrogens or sympatholytic drugs. Whatever the mechanism, this annoying side effect of the drug has continued to be the chief deterrent to its continuous use in dosage adequate to produce sizable hypotensive effects.

Dosage of *V. Viride* in Hypertension

The dosage of *V. viride* in the chronic treatment of hypertension is extremely critical. Thus, little or no effect may occur after a certain dose when an increase of 10 to 20 per cent above that dose may cause definite or even profound effects. This is an unfortunate characteristic of the drug from the practical point of view, since it necessitates the greatest of care on the part of both patient and physician to establish a symptom-free therapeutic dosage

schedule. Moreover, the dosage requirements may vary considerably from patient to patient, so that only by cautious trial of increasing doses can the proper schedule be established for a given patient.

In this clinic it has been found that the most satisfactory mode of administration is by mouth, four or more times a day. This is because the drug is apparently eliminated slowly, so that to obtain a continuous smooth effect, overlapping of dosage is required. Thus, on continuous administration the action of the drug begins to appear about half an hour after a dose, reaches its peak at about two hours and diminishes over the next five to eight hours. By administration every three to five hours in smaller than therapeutic doses, an effective level of the drug may be established without producing peaks that may cause nausea, vomiting or excessive hypotension.

The drug is better tolerated after meals and at bedtime, confirming clinically the experimental observations in animals[10] and man[7] that it is less nauseating when taken on a full stomach or while the patient is lying down, or both. On the other hand, eating at the peak of the drug's activity may induce nausea and vomiting, which otherwise would not occur. Therefore, it has seemed wiser not to administer the drug oftener than every two hours nor to eat within three hours after taking it. Preliminary trial of Dramamine (50 mg. before each meal) for relief of nausea, has apparently given aid in a few patients,[19] but none in others.

All the preparations of *V. viride* so far available have produced more or less nausea and vomiting, and it seems fair to say that this has been the chief objectionable feature of the drug. Of course, there is the hope, though without evidence to date, that chemically pure or altered compounds will produce less nausea and vomiting while retaining their hypotensive properties. Also there is the possibility, which is supported by preliminary observations, that slow-dissolving preparations of the drug will have less emetic action associated with their hypotensive effects. On the other hand, a certain degree of this (or some other) relatively harmless side effect may be a desirable safeguard against collapse or even fatal hypotensive reactions to the drug. So far, there have been no known deaths attributable to oral overdosage with *V. viride*.

In the successful therapeutic use of *V. viride* in essential hypertension probably the most important single requirement is persistent, though cautious, trial of the drug in various dosages over a period of at least weeks or months. During this time the physician and the patient should take the long view of the trends of disease under Veratrum therapy, and not concentrate their attention on any temporary change, whether favorable or unfavorable. In the first place, at least three or four weeks are usually required to establish a proper dosage schedule and to obtain the maximum of hypotensive action with the minimum of side effects. If, after this time, a patient for no apparent reason should lose his hypotensive response to the drug, the dosage should be cautiously increased. Or if, as is more likely, at least on Veriloid, he should become nauseated or have an excessive hypotensive reaction, he should try reducing, not omitting, the offending doses. Incidentally, if such distressing effects appear, the patient should lie down, and if this does not bring relief, he should call his physician. Sometimes merely changing the schedule to a more frequent administration of smaller doses may relieve side effects while retaining the hypotensive response. Although such meticulous adjustments of dosage admittedly are a nuisance, many patients seem to require them to obtain a symptom-free hypotensive effect from the drug.

Summary

Veratrum viride is effective in moderating the arterial pressure in essential hypertension. The oral preparations presently available may produce nausea, vomiting and even collapse unless extreme care is taken with the dosage, and occasionally may do so in spite of such care. Purified extracts and pure alkaloids have been produced for experimental trial, and may eliminate some of these objectionable side reactions. However, in any of its present available forms, *V. viride* is far from an ideal or a curative medicinal agent in essential hypertension. Nevertheless, it seems worthy of further investigation.

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TOTAL AVULSION OF THE SCALP

Report of a Case

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MANY cases of total avulsion of the scalp have been reported in the medical literature, and the treatment has been extremely varied. Formerly, these large wounds were allowed to granulate and gradually to epithelialize spontaneously from the edges. The wounds became severely infected, and the healing period was greatly protracted. Many of the patients treated in this fashion became debilitated from chronic sepsis; some suffered osteomyelitis of the calvarium, and others intracranial complications by extension of the infection through diploetic channels. The end result in those who survived was poor, the thin scar epithelium constantly breaking down, and the contracting scar tissue creating marked deformities of the eyelids.

Replacement of the avulsed scalp has been attempted on numerous occasions but the result, as might have been expected, has been a total failure. The replaced scalp becomes a hard, leathery, nonviable cap, with infection beneath it, which eventually sloughs and causes unnecessary delay. It may be possible, however, to replace a scalp trimmed of all fat and galea with some degree of success, but one should not expect hair growth if replacement is successful.

All possible methods of skin transfer have been attempted with varying degrees of success.

Pinch grafts have been placed on these large wounds with successful epithelialization. However, here again, the healing time has been greatly prolonged, and the end result unsightly not only on the head but also on the rest of the body.

Full-thickness skin grafts have been used, but the results have been poor and the donor sites have presented a problem in covering.

Pedunculated flaps and ropes have been employed, but the procedures have been complicated, drawn out and, in the light of present-day knowledge, entirely unwarranted except in cases with an associated loss of bone that must be replaced, or in neglected cases.

With the development of split-thickness grafting, the results have been more satisfactory. However, it has taken many years for confidence in primary

A B

FIGURE 1. *Appearance of the Wound Approximately Forty-Eight Hours after the Injury. Massive wet penicillin dressings were applied up to this time. The wound is exceptionally clean, and there is no evidence of infection. The periosteum seems to be intact throughout. The lids have been sutured together to prevent injury to the corneas.*

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skin grafting to replace the conviction that split-thickness grafts would take only on a bed of healthy granulations. At the present time it is generally accepted that the method of choice in the treatment of avulsion of the scalp is primary split-thickness grafting.

FIGURE 2. *Full Drum of Split-Thickness Graft Removed from the Lateral Aspect of the Right Thigh with the Padgett Dermatome and Used to Cover the Region of the Eyelids, Root of the Nose and the Entire Frontal Region in a Continuous Sheet of Skin.*

CASE REPORT

E. C. (M.E. & E. I. 623444), a 22-year-old woman, was admitted to the hospital on June 28, 1948, 2 hours after her entire scalp had been avulsed by a power belt at her place of work.

Physical examination showed a well developed and well nourished woman, who was in fairly good general condition and co-operative, but somewhat drowsy from medication she had received at a previous hospital, where emergency treatment had been rendered.

The temperature was 99.2°F., the pulse 80, and the respirations 18. The blood pressure was 110/60.

A massive wet saline dressing on the head was removed for inspection of the wound, which revealed that the entire scalp was missing, exposing the periosteum of the calvarium. The wound reached from, but did not include, ear to ear, and from the root of the nose to the nape of the neck, with the exception of a small triangular flap of remaining scalp on the right occipital region, which appeared quite viable. The skin was missing from both upper lids, exposing the orbicularis muscle, and the right upper lid was lacerated at its medial end. Examination of the eyes disclosed no injury. Emergency examination of the blood revealed a red-cell count of 4,360,000, with a hemoglobin of 8.8 gm. per 100 cc. Urinalysis was essentially normal.

In view of the patient's co-operativeness and the absence of shock, it was decided to clean up the wound somewhat at the bedside. She was given morphine and tetanus antitoxin, and penicillin therapy, 100,000 units every 3 hours, was started immediately. The wound was gently irrigated with saline solution; the lacerated lid was repaired, and the remaining occipital scalp flap sutured back in its proper position. The upper and lower lids of both eyes were sutured together to protect the corneas after local infiltration with 2 per cent procaine. A massive wet penicillin dressing, 1000 units per cubic centimeter, was applied to the wound, and general supportive therapy was administered, including a transfusion of 500 cc. of whole blood, fluids and sedation. The patient's condition on the following day was good, examination of the blood revealing a red-cell count of 4,760,000, with a hemoglobin of 13.8 gm. per 100 cc., and a white-cell count of 12,200. The total protein was 6.1 gm. per 100 cc. She was given another transfusion of 500 cc. of blood in preparation for operation, which was performed on the 3rd day.

Under nitrous oxide, oxygen and ether anesthesia, administered intratracheally, the dressing was removed, and a more detailed examination was possible (Fig. 1). The wound appeared to be clean, with no evidence of infection. A culture taken at this time from the occipital region later grew out *Escherichia coli*, and from the right parietal region no growth was reported. The periosteum everywhere seemed to be intact and uninjured. The small occipital hair-bearing flap appeared in good condition. A full drum of split-thickness graft was removed from the lateral aspect of the right thigh with the Padgett dermatome and used to cover the

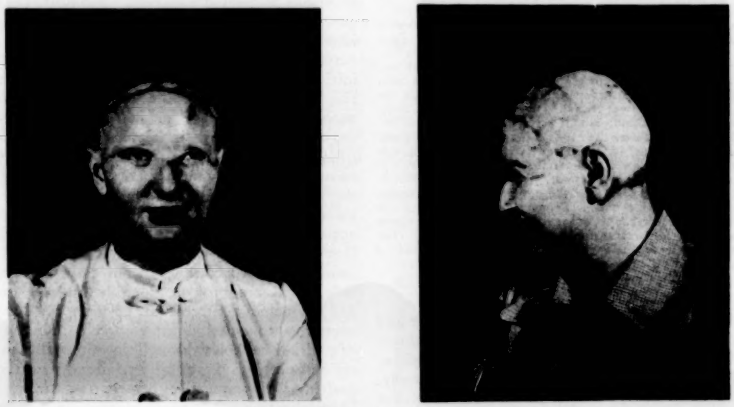
A B

FIGURE 3. *Postoperative Appearance of the Patient.*

On the twelfth postoperative day examination revealed approximately 95 per cent "take" of the skin grafts. In the left frontal region may be seen an area that was not successful, owing to injury to the periosteum that had not originally been detected. This area was very slow in healing but gradually epithelialized over from the edges after the exposed bone had been chiseled down to the bleeding points.

region of the eyelids, root of the nose and the entire frontal region in a continuous sheet of skin (Fig. 2). Four more complete drums of skin grafts taken from the thigh and abdomen successfully covered the entire wound. Pressure dressings were applied to both donor and recipient areas. During the operation the blood pressure remained relatively stable at approximately 110/60 with the administration of 500 cc. of blood.

Postoperatively, another transfusion and fluids were given, and penicillin was continued in the preoperative dosage. The temperature remained normal, and on the 4th postoperative day, the penicillin dosage was reduced to 100,000 units every 8 hours. On the 7th postoperative day, because of the patient's apprehension about her vision, the sutures were removed from the lids, allowing her to open her eyes. On the following day the entire head dressing was removed, revealing that the skin grafts had been approximately 95 per cent successful. The areas not covered were located over the vertex, at the nape of the neck, at the suture lines of the skin grafts and a small area over the left frontal bone (Fig.



A B

FIGURE 4. *Appearance of the Patient's Head Four Months after the Operation. The color of the skin on the frontal region blended well with that of the face.*

A B

FIGURE 5. *Appearance of the Patient with Her Transformation and with Eyebrows Penciled on Her Forehead. There is no retraction of the eyelids, and the excellent result of a single large dermatome graft across the forehead is illustrated.*

3*A* and *B*). On the 12th postoperative day wet penicillin dressings were applied to clean up these areas in preparation for regrafting. The unsuccessful area in the left frontal region now showed exposed bone about the size of a dime. Evidently the periosteum here had been injured at the time of the accident, and this fact had escaped notice previously. On the 15th postoperative day, these areas were covered with free-hand split-thickness grafts under Sodium Pentothal anesthesia intravenously. The exposed bone in the left frontal region was chiseled in an attempt to stimulate granulation, and a skin graft laid over this region also. Penicillin therapy was again begun, and after 5 days the dressing was taken down, revealing most of the grafts floating freely in pus, with only about a 10 per cent successful implantation, the graft over the exposed bone having completely disappeared. Healing of these raw areas thenceforth was slow despite various local applications. However, the wound had healed sufficiently approximately 6 weeks after the accident to enable us to discharge the patient from the hospital and follow her in the office. Spontaneous epithelialization was not complete for 1 more month. As soon as this occurred, she was fitted for a transformation (Fig. 4 and 5). The patient is now ready to go back to work and has made a satisfactory adjustment to her ill fortune.

Discussion

Our experience with the case reported above and with similar cases reported previously by Kazanjian and Webster,* has left us with several impressions. Re-epithelialization should be performed early. The wounds, at this stage, are contaminated but not infected; therefore, concentrated efforts should be made to keep them free from infection. Under these circumstances, one is able to apply a skin graft to the entire calvarium at one operation, with prospects of complete success. Secondly, the emergency local treatment of these wounds is of extreme importance. The first physician seeing the patient may determine the length of hospitalization by his initial dressing. Ointments or escharotics diminish the possibility of successful early skin grafting. A massive wet saline or penicillin pressure dressing seems to be excellent in keeping these wounds free from infection. Thirdly, the antibiotics are of much value, both locally and systematically. However, one should not depend too heavily upon them and thereby put off early operation. Fourthly, one cannot expect a split-thickness graft placed on a portion of calvarium that has been denuded of periosteum to be successful. In our cases, fortunately, only small areas of denuded bone have existed, and to achieve success at covering, it has been necessary to chisel down to freely bleeding bone or to drill burr holes through the outer table through which granulations spring up. Finally, early skin grafting will unquestionably shorten the period of hospitalization. In the case presented above the patient was discharged from the hospital within six weeks.

*Kazanjian, V. H., and Webster, R. C. Treatment of extensive losses of scalp. *Plast. & Reconstruct. Surg.* 1:360-385, 1946.

THE USE OF TANTALUM GAUZE IN THE REPAIR OF HERNIAS WITH TISSUE DEFICIENCIES*

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In 1889, Edward Bassini, of Italy, in prefacing his report on 251 cases of inguinal hernia, said: "After all that has been written with such feverish diligence up to the present time concerning the radical cure of inguinal hernia, it would certainly appear hazardous to publish something further on the subject." In spite of such modesty, his paper marked an epic step forward in the radical cure of hernia, and his operation, or one of its modifications, is most extensively used even today. As a result of the contributions of Zimmerman, Anson, McVey, Ramos, Burton, Harkins, Mattson, Rienhoff, Andrews and others, the anatomic relations of the inguinal canal are better understood, and the time has long passed when the Bassini operation offered the best chance for the surgical cure of inguinal hernia, as has been attested to by Rothschild, Singleton, Mattson, Ferris, Bean, Zimmerman and Iason.

The need for a high ligation of the indirect sac, the importance of tightening the internal inguinal ring, the myth of the conjoined tendon, the destructive effect of suturing functioning muscle to a rigid Poupart's ligament and the effectiveness of the transversalis fascia in repairing a direct inguinal hernia have been so well described by previous writers that the reader is referred to the bibliography for a further discussion of these facts.

In 1948 Throckmorton reported on the use of tantalum gauze in the repair of hernias complicated by tissue deficiency. His series included 14 inguinal hernias in which he used a 50-by-50 weave 3-mil tantalum-wire mesh.

The present paper contains a further report on the subject in which a similar material was used in repair of 61 hernias complicated by tissue deficiency, with a two-year follow-up study. Ten of these were incisional, and 51 were inguinal hernias. During the same period 420 inguinal hernias were repaired without the use of tantalum gauze, indicating that the need for the use of this material is limited to a relatively small number of hernias.

The follow-up study of these cases is not considered adequate in view of the short time that has elapsed. It is an established fact that recurrences may ap-

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pear after five years. This preliminary report can do no more than establish the fact that tantalum is well tolerated by the tissues and that it is readily available and easily handled, and markedly increases the tensile strength of fascial layers to which it is sutured.

The manufacturer's description of the substance is as follows:

> Tantalum, in contrast to stainless steel and vitallium, is not an alloy, but an element (with the symbol of Ta, an atomic number of 73, and an atomic weight of 180.88). Chemically, it approaches glass in resistance to acid and alkalies. These characteristics make this element likely to be inert in the physiochemical environment of animal tissue. Much clinical and experimental evidence seems to bear out this supposition. In addition, tantalum possesses high tensile strength, ductility and malleability, qualities that make the handling relatively easy. The strength of the unannealed tantalum is similar to that of cold, rolled steel. It can be drawn into fine wire, and the wire woven into a cloth, gauze, or screen. It becomes work-hardened at a much lower rate than most other metals used surgically. It has a high degree of tissue acceptability, so that in soft or on bony tissues, the cellular response causes firm adhesion of the tissues to the tantalum. Being insoluble in tissue fluids, toxic dissolution products of tantalum are not encountered. With tantalum, electrolytic action in body fluids is reduced to the minimum. Tantalum gauze consists of tantalum wire, .003 inch diameter, which has been woven into a 50 by 50 mesh. Sheets of this material measuring six inches by twelve inches are supplied for surgical purposes. To prepare the mesh for surgical use, it should be thoroughly scrubbed with soap and water, rinsed thoroughly, and then sponged off with either ether or alcohol. It is then sterilized by autoclaving.

Indications

Tissue deficiency constitutes the primary indication for the use of tantalum gauze. The repair of any hernia is a simple procedure if adequate fascial structures are available for sound anatomic correction. Unfortunately, these tissues are not always sufficient, and surgeons have taxed their ingenuity in attempts to provide substitutes for an attenuated or absent transversalis fascia. The use of cutis grafts has been reported by Lowe, Uihlein, Cannaday, Swenson, and Scola. Autogenous sutures have been used by McArthur, Kirschner, Gallie and LeMesurier. Transplanted patches of fascia lata have been described by Singleton and Stehouwer. Wangensteen has utilized pedicle grafts, and Chaudy reported the use of preserved heterogenous grafts in hernia repair.

The implications of the reports of these surgeons are obvious. In spite of all available methods for hernia repair, cases are constantly being seen in which recurrence is almost certain unless the surgeon selects some measure that will further strengthen the local structures. A failure to recognize this need is undoubtedly responsible for a definite number of recurrent hernias. Of all methods for reinforcing Hesselbach's triangle described in the literature, it seems that none is so simple as tailoring a piece of tantalum gauze to fit the defect. Its tensile strength cannot be doubted; its ease of handling is easily demonstrated, and experience has shown it to be well tolerated by the tissues.

As might be expected, surgeons who are not familiar with this use of tantalum gauze are instinctively cautious in adopting a new measure until its safety has been demonstrated. It is for this reason that such reports as this are necessary.

Tissue Tolerance

As mentioned above, there is every evidence that tantalum gauze is well tolerated by the tissues. The amount of induration in the wound after operation is comparable to that found in the usual hernia repaired with cotton. No febrile reaction is noted that can be attributed to the presence of this foreign

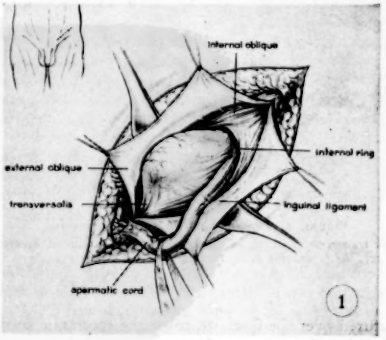

Figure 1. *Appearance of a Direct Inguinal Hernia. The direct hernial sac is seen protruding from Hesselbach's triangle, with an attenuated transversalis fascia.*

body. All wounds in my series healed by first intention, and the sutures were removed on the fifth postoperative day. I am convinced that the implantation of tantalum gauze causes no subjective discomfort immediately after the operation or months later. In the earlier cases of this series, care was taken to place the gauze in the wound so that such structures as the spermatic cord and the iliohypogastric nerve would not come directly in contact with the tantalum. As additional experience was gained with this material, it was found that this precaution was not necessary. The spermatic cord or the iliohypogastric nerve may lie in direct contact with the tantalum gauze without causing any untoward symptoms. Furthermore, a decided advantage in the use of this material is the fact that it may be employed anywhere in the inguinal region where weakness is evident. If the transversalis fascia is absent, or greatly attenuated, it may be

fashioned to cover this structure, being sutured to the inguinal ligament (Poupart's ligament) or Cooper's ligament as desired. If there is a deficiency of the lower end of the external oblique muscle in the presence of an unusually large external inguinal ring, it is sometimes difficult to cover the cord with fascia and thus to preserve the obliquity of the inguinal canal. In such cases tantalum gauze may be

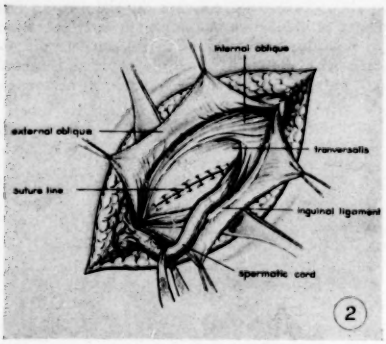

FIGURE 2. *Repair of a Direct Inguinal Hernia.*
The transversalis fascia has been plicated over the direct hernial sac, the protrusion being inverted into the abdominal cavity.

sutured over the fascia to cover the spermatic cord. Occasionally, the external oblique muscle is split and attenuated above the level of the internal inguinal ring, and here again it is a simple matter to reinforce the fascia with the gauze wherever necessary. In cases in which there is an unusually large internal ring, one may find it impossible to close it snugly by suturing the transversalis fascia under the spermatic cord. In such cases, tantalum gauze may be so cut as to surround the cord as it lies on the transversalis fascia, thereby reconstructing and tightening the internal inguinal ring. The various steps in the repair of a direct hernia are demonstrated in Figures 1 to 3.

The mortality from hernioplasty is negligible, but as much cannot be said of its morbidity. The time has come when surgeons must concern themselves with any factor contributing to the morbidity of this operation if further progress is to be made. Such factors as time spent in the hospital and time out of work become increasingly important. Articles in current periodicals are informing patients what to expect from such an operation.

A transverse or oblique incision is used, and towels are clipped to the wound margins with Michel clips. It is considered important to carry the incision low down over the pubic spine, so as to ensure a good exposure in this region. After incision of the external oblique muscle, its margins are mobilized and retracted by means of traction sutures, rather than by crushing clamps, which merely clutter up the field. The spermatic cord is next elevated from the bed by sharp dissection including all veins and cremasteric fibers in the retracting tape. If the hernia is of an indirect type, the cremaster muscle is opened and the sac dissected from the cord to a high neck. This is done entirely by sharp dissection. If the procedure is properly performed, only the peritoneal sac is removed, and all the attached structures are left behind. After the neck of the sac is transfixed and ligated at a level where the prevesical fat makes its appearance, the distal portion is amputated and the stump allowed to retract. It is not anchored under the internal oblique muscle as advocated by some writers. Only one other important step remains in the repair of an indirect inguinal hernia, and that is the reconstruction and tightening of the internal ring by suture of the transversalis fascia around the cord. Any attenuation or defect in the transversalis fascia should be repaired at the same time, so as to prevent the development of a direct hernia later on.

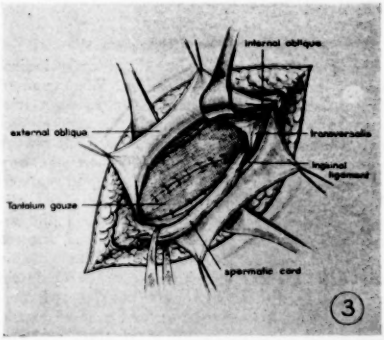

FIGURE 3. *Tantalum Gauze in Repair of a Direct Inguinal Hernia.*
A piece of tantalum gauze has been tailored to fit the floor of the inguinal canal; its margins are sutured to the inguinal ligament, pubic spine and rectus fascia. The spermatic cord will lie on top of the tantalum gauze.

The external oblique muscle is then closed over the spermatic cord, preserving the obliquity of the inguinal canal.

In the repair of a hernia just described, tissue deficiency is seldom observed, and there is no need to use the tantalum gauze.

The direct hernia is likely to present more of a problem, especially the larger variety found in obese men. Here the sac protrudes through Hesselbach's triangle, surrounded by a narrow rim of weakened and attenuated transversalis fascia. The sac in many cases has so dilated the external inguinal ring that there is a large fascial defect in the lower end of this structure. The surgeon is confronted with the problem of closing a triangular opening whose margins are relatively inelastic and widely separated. In the hernia described, relaxing incisions in the anterior rectus fascia are not thought to be always adequate, and some sort of transplant or graft is necessary for a successful repair. The dissection should be carried out so as to expose the edge of the rectus fascia on the medial side and the pubic spine below. The hernia sac is plicated or removed, and a piece of tantalum gauze is cut to fit the defect, allowing 0.6 cm. to be folded in about its margin to permit easier suturing. The gauze is then anchored in place with interrupted sutures of No. 70 cotton placed 1 cm. apart. In the fitting of this implant, it is wise to release traction on the retractors, or the gauze will be too large for the defect to be covered. In my experience enough firm transversalis fascia usually exists about the internal ring to permit its suture to the gauze under the spermatic cord. When the occasion demands, a piece wide enough to extend out over the anterior rectus fascia can be cut. If the inguinal ligament tends to shred or does not appear to be of good strength, the lateral margin of the tantalum gauze can be sutured to Cooper's ligament. This structure is best exposed by incision of the transversalis fascia 1 cm. from and parallel to the inguinal ligament, as described by Farris et al. The external oblique muscle is next sutured over the spermatic cord with interrupted sutures of No. 20 cotton, and at the same time the external inguinal ring is reconstructed snugly about the cord. If defects in this layer of fascia exist, another piece of tantalum gauze can be used to reinforce the fascia wherever needed. The superficial fascia and skin are closed with interrupted sutures of fine cotton.

Such an operation allows for an anatomic repair without tension, and the postoperative comfort attests to this fact.

During the postoperative course, the patient is allowed to stand up to void a few hours after the operation. On the first postoperative day he is encouraged to walk a short distance at frequent intervals. To reduce the incidence of gas pains, he is kept on water by mouth for twenty-four hours and then given a full diet without milk or fruit juice. All wounds in my series healed by first intention, and the sutures were removed on the fifth postoperative day, when the patients were usually discharged, although in the beginning of the series, a few patients were kept a day or two longer for observation. On returning home, they were allowed to go up and down stairs daily and to drive a car at the end of the second week. The patients were allowed to return to work after the third, fourth or fifth week, depending on inclination and type of job. Two recurrences have been observed to date in this group of difficult hernias. Both appeared on one side in patients who had had bilateral repairs with transplantation of the spermatic cord and sacrifice of the obliquity of the inguinal canal. In the earlier cases in this series, I hesitated to allow the cord to lie in direct contact with the tantalum gauze, and to permit the gauze to lie between two layers of fascia — namely, the transversalis and external oblique muscles — it was necessary to transplant the cord. This, of course, caused the new external inguinal ring to be more nearly superimposed on the internal inguinal ring, and it was in this type of repair that the 2 recurrences appeared. In the most recent cases in this group, the cord was allowed to lie directly in contact with the tantalum gauze and the external oblique fascia approximated over the cord, thereby preserving the obliquity of the inguinal canal. This description of the operation and the postoperative care applies only to my cases, which represent 30 of the 51 inguinal hernias. The other 21 inguinal repairs were performed by five other surgeons on the staff at Memorial Hospital, Worcester, each utilizing individual variations in technic.

Ventral Hernia

Although experience with the use of tantalum gauze in the repair of large ventral hernias has been limited, it has nevertheless been highly satisfactory. Its greatest help is in the repair of hernias with such large defects that fascial approximation is either impossible or highly dangerous because of the resulting increased intra-abdominal pressure. The use of this material in ventral hernias has been described by Throckmorton and Koontz. It suffices to say that after the hernia sac has been resected and the peritoneum closed, the fascia about the periphery of the defect is identified and a piece of tantalum gauze sutured in place. One precaution must be observed, however: if the atrophic skin often found over the hernia sac is sutured directly over the gauze with no intervening subcutaneous fat, slough is likely to occur. Care must be taken to resect all atrophic redundant skin, and to cover the tantalum gauze with subcutaneous fat and its attached skin. The ease of such a repair is in striking contrast to the extensive dissection required in the use of the iliotibial tract of the fascia lata as described by Wangensteen.

Summary

The use of tantalum gauze in the repair of inguinal and ventral hernias associated with tissue deficiency offers a safe and convenient means of repairing these defects without tension.

One can reduce the morbidity associated with hernia repair by avoiding the suture of a functioning muscle to an inelastic fascial structure, employing an anatomic repair utilizing fascial layers sutured without tension, utilizing tantalum gauze where tissue deficiency exists and permitting early ambulation.

When the transversalis fascia is reinforced with tantalum gauze, the spermatic cord may lie in direct contact with this material and the external oblique fascia closed over the cord, thus preserving the obliquity of the inguinal canal.

It is believed that tantalum gauze provides a satisfactory method of repair, with little discomfort to the patient, for most large inguinal hernias with tissue defects and that after five days in the hospital, and two or three weeks at home, most patients can safely return to work.

27 Elm Street

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MEDICAL PROGRESS

DERMATOLOGIC THERAPY

John Godwin Downing, M.D.*

BOSTON

PROGRESS in the therapy of cutaneous diseases during the last few years has been tremendous. Dermatologists observing the reactions on the skin have been able to keep other physicians informed regarding the useful as well as the undesirable reactions of new drugs. They have demonstrated that sensitization to these agents affects not only the skin but also important organs of the body. This subject is of vital significance. Few physicians realize the disability, economic loss and suffering that result from sensitization to a drug, varying from the usual two-week period of incapacitation to permanent disability, or even death. Therefore, this factor is a vital one in the evaluation of a new drug.

The first steps in the relief of the patient are the proper diagnosis and the selection of a suitable remedy. The literature is extremely confusing. Many reports are published as a result of enthusiasm aroused by the relief of a few patients with a given substance. The drug is too readily distributed by commercial houses, and if the cure is not corroborated the negative results are seldom published by subsequent investigators. As a result, the product continues on the market at great expense and with little relief to sufferers. Chiefs of busy clinics are deluged with trial supplies of various forms of medication, and it is difficult to separate the wheat from the chaff. For this reason, even the trained dermatologist is apt to become confused if he allows the observation of a few cases to mislead him. He must test out these various remedies in a well organized program.

In the evaluation of a new drug for topical application several factors must be considered. First, what is its advantage over accepted therapy? Has it demonstrated definite bactericidal activity in vitro, and is this activity maintained at various

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temperatures? Does the drug diffuse readily from its ointment bases? How much of the medication is absorbed by the skin? Is it more economical than the accepted medication? If it is expensive, is its cost justified because of the reduction in time of disability and suffering? Is it a sensitizer? Does its use in more or less unimportant local infections sensitize patients and preclude its use in more systemic diseases? All these factors must be considered.

Recognition of the various stages of the cutaneous manifestations of avitaminosis and the influence of the endocrine factor have advanced therapy. The dermatologic world is impatiently awaiting definite confirmation of the underground reports of improvement of cases of psoriasis, scleroderma and severe lupus erythematosus by the administration of 11,17-oxysteroids (Compounds E and F). One preliminary report[1] states that Compound E was given to patients with severe lupus erythematosus, with encouraging results to be reported later. Another résumé[2] mentions that 3 patients with acute disseminated lupus erythematosus showed marked clinical improvement and disappearance of the typical butterfly lesions when given 10 mg. of adrenocorticotrophic hormone (ACTH) intramuscularly every six hours. A remarkable forty-eight-hour recovery from a severe contact dermatitis was observed in a young physician after treatment with ACTH, with a prompt recurrence on the seventh day, when the medication was discontinued.

The introduction of the antihistaminic action was hailed as a welcome addition to therapy. Although the antihistamines have been found of value in some cases of urticaria and dermatitis due to drugs and so-called physical allergies, on the whole they have proved somewhat disappointing, and in other types of eruption even injurious. The same statement has been true of many of the antibiotics. Penicillin was tried extensively in the treatment of conditions such as acne vulgaris but was found to be of little value; in fact, the lesions seemed to become worse as soon as the drug was discontinued. In properly selected diseases, however, it is of definite value, as is true of the other antibiotics. Because of the experience with penicillin, the newer antibiotics are not being used so indiscriminately.

Local therapy in the treatment of cutaneous diseases seems to have a charm for all physicians, as a result of the rapid incorporation of vitamins, hormones, antihistamines and antibiotics in ointments or lotions for topical application.

For information regarding pharmaceutical preparations, more physicians should read the publications of the *Journal of the American Pharmaceutical Association*, where there are valuable reports on the preparation of various drugs related to dermatology. Bhatia and Zopf[3] report on two hydrophilic-ointment bases. A clinical investigation of bentonite-petrolatum ointments and ointment bases has been described by Hollander and McClenahan.[4] They describe bentonite as a clay-like colloidal substance from volcanic ash, possessing swelling properties that are due to its affinity for water. These properties permit detergent action and the absorption of moisture and debris from the skin. Bentonite forms stable salts with organic bases, including alkaloids and proteins. It dries and cracks if used alone, but, incorporated with petrolatum, it is an excellent vehicle for drugs soluble in water or alcohol. With boric acid and a preservative a hydrophilic ointment was made that was excellent for eczematoid dermatitis. I have found a similar compound of value in oozing eruptions of the scalp.

More stable shake lotions can be made by the use of cetyl alcohol combinations as suspending agents. Dean et al.[5] report on a special titanium dioxide lotion that contains 16 per cent zinc oxide and 3.2 per cent titanium dioxide, originally suspended by bentonite magma. By replacing the latter with an aqueous mixture of cetyl alcohol and sodium lauryl sulfate, they obtained excellent improvement in the suspension. These authors achieved similar results by the addition of this combination to Calamine Lotion (*U.S.P.*) and White Lotion (*N. F.*) The formula of this cetyl alcohol stabilizer was prepared as follows:

Substance	Amount
Cetyl alcohol	36 gm.
Sodium lauryl sulfate	4 gm.
Distilled water	qs 1000 cc.

Many new remedies are constantly being recommended for the treatment of scabies. Robinson[6] reports only 1 failure in 71 cases treated with the following:

Substance	Amount
	%
Tyrothricin	0.05
Benzyl benzoate	30.0
Benzocaine	3.0
23 H. alcohol (ethyl)	65.0
Distilled water and flavoring agents	qs 100.0

Owing to the fact that many cases of scabies are complicated by pyogenic infection, I can see the value of tyrothricin, but fail to appreciate the addition of benzocaine, which is a well known sensitizer of the skin and which therefore may cause unfavorable reactions on future exposure to useful chemically related drugs. Cannon and McRae[7] recommend Kwell (hexachlorocyclohexane) in the treatment of scabies, reporting 100 cases treated with one to three applications without irritation, discomfort or sensitization. Crotonyl-n-ethyl-o-toluidine ointment[8] (Eurax) has also been found beneficial in the treatment of scabies.

A new body deodorant is reported by Darnell[9] as a very useful therapeutic agent. Six hundred and forty subjects were tested with a formula con-

taining 0.12 per cent potassium mercuric iodide, 0.25 per cent sodium hydroxide and 0.02 per cent potassium iodide in distilled water. The solution was evidently nonsensitizing when applied to the human skin and had definite deodorizing quality.

When one considers the many causes of pruritus ani and pruritus vulvae it is difficult to be impressed with the value of treatment with a single remedy, such as an ointment. Driver et al.[10] had successful results in patients treated only with iso-par co-paraffinate ointment. In 71 per cent of 41 cases cure or symptomatic relief was obtained with the ointment alone. With the addition of x-ray therapy there was cure or symptomatic relief in 85 per cent of 127 cases. In my experience, unless the cause is found, few patients remain well despite any local therapy. This ointment is apparently of value at orifices. Walker[11] reports a cure of 60 per cent of 41 uncultured cases of otitis externa treated with iso-par. The ear canal was cleansed with alcohol applicators, and a thin coating of the ointment applied. This was repeated later at home by the patient.

The possibility that Promin jelly* is of value in skin tuberculosis is suggested by the excellent results obtained by Garb,[12] who treated a Negro with three lesions that had failed to respond to x-ray therapy. The lesions healed in seven weeks with the application of 5 per cent Promin jelly three times daily.

Sulzberger and Baer[13] report that Vioform is of value in dermatoses when a mild, nonirritating, antibacterial and antifungicidal effect is necessary; these include eczematous eruptions, atopic dermatitis, psoriasis, seborrheic dermatoses, pruritus ani or vulvae and sycosis vulgaris. Vioform is also useful as a general soothing and antiseptic agent. The authors state that it occasionally causes sensitization in 5 per cent strength, but rarely in 3 per cent strength.

Kurtin and Yontef[14] report on five years' experimentation on photosensitization therapy of acne vulgaris, selecting the following photosensitizing formula as the most successful:

Substance	Amount
	%
Crude oil tar	5
Sulfur	5
Sulfathiazoie	5
Lanolin and Lassar's paste aa ad	

Crude coal tar should not be used in pyogenic infections, and dermatologists avoid the application of sulfathiazole in any cutaneous therapy. Lastly, photosensitization of the skin is a risky procedure.

Tar is still a popular drug in dermatology. Berenblum[15] found that liquor picis carbonis consisting of 20 per cent crude coal tar in ethyl alcohol possessed carcinogenic properties for mouse skin. He advised that it would probably be wisest to avoid its long-continued application. Cancer of the anus due to the prolonged use of tar locally for pruritus ani has been reported.[16]

The report of sensitization to monoglyceryl para-aminobenzoate is of value because of the widespread use of this drug as a filter of erythema-producing rays in sunlight. Baer and Meltzer[17] report the case of a forty-eight-year-old man who developed two attacks of allergic contact dermatitis from the use of this drug as a sunburn preventive. This was proved by a strong patch-test reaction to the drug and negative reactions to the other ingredients in the compound. The patient was also sensitive to related chemicals — benzocaine and sulfonamide.

Sullivan[18] has continued his studies on podophyllotoxin. Results in another series of patients with condyloma acuminatum treated with a 20 per cent concentration of resin of podophyllum in 95 per cent alcohol were superior to those obtained with the oil suspension, much of which spread from the surface of the warts to the adjacent normal tissue. The tincture penetrated the crevices of the surfaces of the tumors and confined itself precisely to the tumors, if it was applied accurately in small amounts. Cures resulted in 15 of 100 patients with verruca vulgaris who were treated with the resin in alcohol. Podophyllotoxin was the only component capable of curing the genital warts. Topically applied to the skin and benign epithelial tumors, it produces severe cytotoxic effects and interference with mitosis, resulting in distorted mitotic patterns. Of the presently available components of the resin, podphyllotoxin is apparently the one principally responsible for the production of the abnormal cellular alterations.

Reich et al.[19] give a very practical review of the method of application of podophyllin. They emphasize the following local and follow-up precautions: the adjacent normal mucous membrane and skin are protected by a soothing anesthetic ointment; the patient must get into a bathtub within four to eight hours and thoroughly wash off the podophyllin with soap and water. Discomfort may follow for several days, and the patient must be warned of this. A great measure of relief can be given if local anesthetic ointments are further applied. Usually, one application of podophyllin suffices; rarely are two or three needed. If further podophyllin is required it should not be applied before one week after the first application — preferably two weeks.

At the last meeting of the American Dermatological Association the value of podophyllin in the treatment of cancer and keratoses was discussed. Smith and Garrett[20] showed some excellent cosmetic results of treatment with this drug.

Having seen cases of near gangrene from the use of a preparation containing 50 per cent each of phenol and camphor, recommended in 1941

*Promin is a sulfone derivative with complex formula; the jelly consists of Promin (5 per cent), tragacanth (3 per cent), propylene glycol (10 per cent) and water (80 per cent).

by Francis[21] in the treatment of athlete's foot, I appreciated the excellent review of Deichman[22] on the local and systemic effects following skin contact with phenol. This article, which cites several deaths after such contact, should be read in its entirety.

Many true and tried dermatologic remedies have fallen into ill repute because of the untoward reactions following their use. Ammoniated mercury was formerly one of the most frequently used substances in the treatment of psoriasis. Salicylic acid has been used with ammoniated mercury to promote absorption of the mercury salt. This combination has caused many severe skin irritations. Huyck[23] has shown that this result depends greatly on the amount of salicylic acid used in this combination, and quotes Siemens and Schreiber,[24] who found that equal weights of salicylic acid and ammoniated mercury in an ointment base produced mercuric chloride, mercuric salicylate and ammonium salicylate, which are irritating when applied to the skin. A justifiable conclusion is that when these two substances are indicated, the amount of salicylic acid should be reduced to half that of the mercury content.

Hopkins and his co-workers[25] offer useful suggestions for the treatment of hyperhidrosis and symmetric livid areas of the feet. They found that the best results followed foot baths of 4 per cent potassium alum, 4 per cent formaldehyde painted locally and tannic acid ointment (10 to 20 per cent in carbowax). Twenty-five per cent exsiccated potassium alum and 75 per cent talc were best for prolonged treatment. Any therapy that will improve this condition is most welcome.

Lerner[26] elaborates on an old treatment for removal of tattoo marks. While the tattooed surface is kept moist with 100 per cent tannic acid, fine incisions are cross-hatched on it. The area is then rubbed with a silver nitrate pencil and dressed. In fifteen to twenty-five days the brown eschar spontaneously separates, removing the tattoo marks.

Benson[27] reports further good results from the treatment of ammonia dermatitis, or diaper rash, with Diaparene (para di-isobutyl-cresoxy-ethoxy, ethyl di-methyl benzyl ammonium chloride monohydrate), 1:25,000. Rinsing of the diapers with this chemical proved it to be safe, effective, nonirritating and nonsensitizing.

Surgeons should be interested in the germicidal use and value of hexachlorophene. A report[28] on this compound states that G-11 (hexachlorophene) when tested in the form of its sodium or potassium salts was strongly bacteriostatic and bactericidal against *Staphylococcus aureus* and other gram-positive cocci such as the *Streptococcus haemolyticus* (Type C) and *Str. viridans*. It appears that G-11 is equally effective in soap and in emulsion. According to a recent report from the Mercy Hospital in Toledo,[29] this substance in pH isoderm has been used for almost a year with satisfaction. At the Peter Bent Brigham Hospital this technic has also been used as a prophylactic measure in the nursery and for those who handle food in the hospital kitchens. It has been stated that pathogenic staphylococci disappear from the skin of carriers after one week's use of G-11.[30]

In the treatment of fungous infections of the skin there have been no recent worthwhile additions to therapy. The use of the fatty acids has been somewhat disappointing. The original concept of fatty acids in the treatment of fungous diseases was derived from industry, where they were employed to prevent mold. Fatty acids are derived by hydrolysis of the neutral fats, which are triglycerates of the fatty acids. The acids with less than four carbon atoms are soluble in water in all proportions, and there is a gradual decrease in solubility as the number of carbon atoms increase. Thus, the propionic compounds are soluble in water, whereas the undecylenic acid compounds are not.

Fatty acids are effective fungicides against tinea capitis. Since they are physiologic in action, they are not irritating. They are also bactericidal against *Staph. aureus* and streptococci. Murphy and Rothman[31] proved that the human body produces an odd number of fatty acids believed to be derived from the intermediate metabolism of proteins. He collected 45 kg. of hairs and isolated from them the odd-numbered fatty acids. These were found to have a selective fungicidal action against *Microsporum audouini*, and this explained adequately for the first time the spontaneous cure of tinea capitis at puberty. There are no sebaceous glands on the soles and sides of the feet, and it is here that the fatty acids are the most effective fungicides. These same agents are not too effective against tinea corporis. It has been shown by experimentation that where sebaceous glands are located, the body builds up a resistance to the fatty acids and that they are thus less effective fungicides.

New compounds are constantly being introduced, some in well controlled experiments and others in studies not so well done. Sperber[32] reports 80 to 90 per cent clinical cures with the unusual therapy of local application of whale oil alone and in combination with trichophytin, with the addition of autoserum injections in stubborn cases. This report needs confirmation. McGavack et al.[33] describe the use of tetra-chloro-para-benzoquinone, a substance employed to control fungi that attack seed. It was used as an ointment (5 to 50 per cent) and as a powder (undiluted and diluted with equal parts of powdered talc). There were 28 per cent cures in 84 cases of tinea capitis due to *M. audouini*. Treatment of 20 cases of tinea cruris and pedis gave inconclusive results.

Felsher[34] reports the use of 5 per cent salicylanilide in carbowax 1500, with cure of 105 cases out of 150 subjects infected with this organism. He concludes that this drug is superior to all others.

Behling and Markel[35] discuss the recent epidemic and management of ringworm in Indiana. The treatment and public-health measures were as follows: 5 per cent salicylanilide, 1 per cent hyamine 1622 and carbowax 1500 was rubbed into the scalp for five minutes daily; and 10 per cent copper undecylenate, 5 per cent undecylenic acid, 1 per cent aerosol O.T. and carbon tetrachloride was applied daily to the scalp with a toothbrush. (The Food and Drug Administration considers carbon tetrachloride too toxic, and a different solvent was later substituted.) The infected children were treated daily at school with the ointment or liquid, and fluorescent hairs were plucked out. Their hair was clipped every two weeks in school. Barbers were educated regarding the sterilization of instruments, and the use of neck dusters and brushes was forbidden. The backs of theater seats were cleansed at night, and newspapers were placed on them for the children. Many seats contained infected hairs, and theater managers were instructed in the use of Wood's light. Twenty of two hundred seats contained hairs that on culture showed *M. audouini*.

Iodides have demonstrated their value in the treatment of systemic mycotic infections. They are specific for sporotrichosis, and Fowle and Georg[36] have shown that they are of value in the treatment of suppurative ringworm contracted from cattle.

Kinnear and Rogers,[37] reporting on ringworm of the scalp in East Scotland, state that epilation by x-rays or thallium is the most rapid and successful means of cure. The use of thallium acetate so frequently has a serious aftermath, even death, that it should be used with extreme caution.

In a review of the foreign literature it is apparent that the local use of the sulfonamides and penicillin compounds is still fairly popular. Evidently, physicians abroad have not as yet had the percentage of sensitization reactions experienced by American physicians. Carpenter[38] reports remarkable healing in a brother and sister suffering from familial benign chronic pemphigus following the use of penicillin locally and orally. In my experience, these lesions respond to any local treatment, but in due time recur.

A scientific article on the use of penicillin cream in sycosis barbae considers the association of the same type of *Staph. pyogenes* present in the nose and in lesions on the face. The authors[39] conclude that penicillin cream is effective in controlling this disease, provided the organism is penicillin sensitive. However, they fail to consider the sensitization feature of penicillin, which has been a deterrent to its continued use by American dermatologists. Griffin et al.[40] confirm the value of penicillin in the treatment of cutaneous anthrax. They treated 17 cases with 12,900,000 units, with cure of all cases. Patients having face and head lesions also received sulfadiazine. One patient had meningitis and received antianthrax serum.

Rubin and Bland[41] report 2 interesting cases of Weber–Christian disease treated with the new antibiotics. One case apparently responded to penicillin, after failure to respond to streptomycin. The second patient, who received 1,620,000 units of penicillin, showed some improvement but continued to have periodic episodes with the appearance of new lesions. As the result of this response the authors believe that these cases fall into the category of an infectious process of undetermined origin. They cite the causes of this disease as iodides and bromides, foci of infection, avitaminosis, disturbance of fat metabolism, an undetermined specific infectious process and bacterial allergy.

Streptomycin, despite its occasional untoward reaction on the eighth nerve and the skin, is being used with good effect in an increasing number of serious diseases. It will be unfortunate if the local use of this drug in the treatment of unimportant, self-limited cutaneous infections causes sensitization, which may prohibit its subsequent use in more serious infections. Large dermatologic clinics are now busy testing streptomycin and dihydrostreptomycin and other antibiotics for their value in local therapy, and are finding that such use is sensitizing certain susceptible persons.

Falk[42] reports the cure of a case of water-borne tularemia, occurring in a twenty-three-year-old man who had scratched his hand while cleaning fish. A typical reaction, with a high agglutination titer, developed. The use of streptomycin, 0.2 gm. intramuscularly every three hours for seven days, brought prompt results. This is the second case of water-borne tularemia to be reported.

Three cases clinically typical of chancroid were treated by Jawetz[43] with streptomycin, 0.5 gm. intramuscularly daily for five days. The lesions in all cases healed in five to fourteen days, and buboes when present healed shortly after. He quotes from other reports to the effect that of 15 cases treated with streptomycin, only 1 relapse occurred in a follow-up period of sixteen to forty-five weeks. The use of streptomycin has been reported in chronic granuloma inguinale by several groups.[44, 45]

Devine et al.[46] describe a case of rhinoscleroma apparently cured with streptomycin. The patient, a twenty-two-year-old woman born in Siberia, was regarded as having rhinoscleroma in 1938 in Shanghai and was unsuccessfully treated by several methods. When she was seen in 1946 there was obstruction of both nostrils, and the pharynx, epiglottis and larynx were involved with granulomatous growths. Streptomycin, 250 mg.

intramuscularly every three hours, was discontinued after one week's use because of a sensitivity reaction. It was resumed twelve days later and continued for forty-three days, at which time there was a clinical and bacteriologic cure. Eight months later there was no activity; cultures were negative, and the cicatricial stenoses of the nostrils were surgically repaired. Cure of a case of keratosis blennorrhagica with streptomycin, after previous ineffectual treatment with penicillin and sulfonamides, has been reported by Thompson and his associates.[47]

Research workers continue in their search for new antibiotics of species of streptomyces, as shown by the two isolated from oats, flax and wheat.[48] They are culture filtrates; both are active against gram-positive and gram-negative organisms, but their high toxicity precludes their therapeutic use. Combes et al.[49] summarize the value and limitations of streptomycin in dermatology. They state that streptomycin is the antibiotic of choice in granuloma inguinale, tularemia and skin infections due to *Pseudomonas aeruginosa* and that it is of definite value in tuberculosis colliquativa, tuberculosis orificialis, chancroid, infectious eczematoid dermatitis and cutaneous infections when other antibiotics have failed or are not tolerated (it may benefit other forms of cutaneous tuberculosis, rhinoscleroma and leprosy). Systemic toxic reactions are not rare, and they may be serious and usually appear after weeks of therapy; vertigo may be severe and permanent. Finally, skin reactions are of three types: an early polymorphous type of exanthema appearing before the tenth day of treatment, which responds to antihistaminics and does not require cessation of therapy; exfoliative dermatitis, appearing after many weeks of therapy; and contact dermatitis, which is of high incidence, particularly in those handling the streptomycin.

Calciferol has been of great value in the treatment of lupus vulgaris. However, not all cases respond to this medication alone. Recent work has demonstrated that the addition of streptomycin is effective in this type of case, as shown by the excellent results obtained by Cornbleet[50] in 5 cases. However, even this combination does not produce a complete cure, as indicated by biopsies taken after treatment.

Pincoffs et al.[51] report the use of Chloromycetin in 5 cases of the Eastern form of Rocky Mountain spotted fever. The initial dose was 75 mg. per kilogram of body weight, and 0.25 gm. was administered orally every three hours. In all cases the temperature was normal seventy-six hours after the initial dose, and there were no recurrences when the drug was discontinued after twenty-four hours of normal temperature. There was no mortality in this group.

Spink and his co-workers[52] discuss the use of aureomycin in human brucellosis. The drug was administered orally daily in 24 cases, and in the follow-up examination one to three months later, blood cultures were positive in only 3. All subjects had fever, which disappeared two or three days after treatment was instituted. The course of treatment covered nine to fifteen days, and only 2 patients required more than one course. The drug should be started in small dosage and increased to 2 to 6 gm. daily. The immediate clinical results from aureomycin surpass those from any other drug, including sulfadiazine and streptomycin.

Pemphigus has been treated with aureomycin. Despite fairly large doses in my clinic I have had more or less indefinite success. At first the patients seemed to improve, but later showed no change in the progress of the disease. The response in some cases of herpes zoster is rather dramatic. The side effects noted in man have varied from nausea and vomiting to a metallic taste in the mouth. I prescribed aureomycin for a nursing mother who had considerable pain from involvement of the fifth nerve. Response was immediate; however, there was cessation of the milk from the breasts after she and the nursing infant suffered from diarrhea. O'Leary et al.[53] report 2 cases of acute syphilis in which the patients were treated orally with aureomycin. Results generally comparable to what would be expected with penicillin were obtained. The untoward effects are few. Lennette, Meiklejohn and Thelen[54] discuss pruritus and soreness of the scrotum in 2 patients, and Rose and Kneeland[55] observed 3 cases of transitory vaginitis and a small number of cases of glossitis. They also found 1 case of complete neutropenia in a dermatologic patient after prolonged administration of aureomycin. They conclude that although the expense factor still influences widespread use, aureomycin appears to be the unquestioned agent of choice in brucellosis, lymphogranuloma venereum and possibly granuloma inguinale. They also state that it has been tried in Hodgkin's disease, periarteritis nodosa and lupus erythematosus disseminatus, but without beneficial results.

Finland et al.[56] report on aureomycin treatment of 24 cases of herpes zoster. The drug appeared to halt the progress of the disease and to bring about rapid healing of the lesions. The pain accompanying the acute lesions also subsided after the first day of therapy. The effective oral dosage was 4 gm. daily (1 gm. after each meal and at bedtime) for two to four days, or until the lesions were well dried and encrusted. Half this dose is given for an additional three to five days, and may also be used throughout when the larger doses are not tolerated. Intravenous administration of 500 mg. daily likewise appears to be effective and may

be used if the drug is not tolerated by mouth. The optimum intravenous dosage, however, was not ascertained.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 36141

PRESENTATION OF CASE

A forty-five-year-old Italian-born dye worker was admitted to the hospital complaining of red and slightly painful eyes.

He was well until eight months before admission, when he first noted soreness and stiffness of the knees, ankles and hands without redness or swelling. The symptoms were improved by the application of heat and increased in intensity by wet weather. He took various drugs without improvement. With the onset of warm weather four or five months before admission the joint symptoms were greatly improved, and he had only occasional slight aching of the ankles. During the same period, however, he began to feel tired, and his appetite decreased. Three months before admission he developed pain and redness in his right eye, and a few days later in his left also. He was seen in the Out Patient Department four weeks before admission for his eye complaints. An iritis and keratitis were found. The blood Hinton test was negative. Chest, sinus and dental films were normal. Four days before admission he developed a slight cough, productive of half a cupful of mucoid sputum daily, often containing a clot of bright-red blood. There was no chest pain. He felt tired, lost his appetite, became hoarse and noted a slightly sore throat.

Fifteen years previously, for a two-year period, the patient was quite ill with intermittent diarrhea, severe sweats, weight loss of 20 to 30 pounds and occasional blood in the stools. He was hospitalized twice. He had no pain. A barium enema and gastrointestinal series were negative.

Physical examination showed a well developed, well nourished, pale man who appeared chronically ill. No lesions were noted on the skin. The conjunctivas were injected, and the corneas showed a few peripheral punctate ulcers, with interstitial vascularization at the periphery. The irises revealed mild injection without synechiae. There were no lens opacities. The fundi were normal. The scleras showed inflammation. The tongue was furry and slightly dry. There was slight limitation of motion of the neck to the right, with pain. Other motions were normal. There was slight thickening of the metacarpophalangeal joints, with tenderness bilaterally. The wrists were tender, with slight swelling and pain on extreme degrees of motion. The shoulders were painful on full motion. There were nodules over both elbows. The right knee showed slight thickening of the soft tissues, with slight effusion. No redness or heat of any joint was noted. Examination of the chest demonstrated a high diaphragm on both sides, with limited excursion. Bilateral, fine rales were present at the bases. The heart was not enlarged, and the sounds were of good quality. There were no murmurs. Abdominal examination was negative. The prostate was of normal size with a slightly boggy consistence. A smear of secretions following prostatic massage showed 10 to 15 white cells per high-power field. Neurologic examination was normal.

The pulse was 104, and the temperature was 99.6°F. The blood pressure was 94 systolic, 60 diastolic.

Examination of the blood showed a red-cell count of 3,570,000, with a hemoglobin of 9.1 gm. per 100 cc., and a white-cell count of 12,700, with 71 per cent neutrophils, 25 per cent lymphocytes, 1 per cent monocytes and 3 per cent eosinophils.

Examination of the urine demonstrated a specific gravity of 1.020 with a ++ test for albumin and many white blood cells, hyaline casts and fatty casts in the sediment. A smear of the urine showed no organisms. A few colonies of *Staphylococcus albus* grew on culture. The erythrocyte sedimentation rate was 2.0 mm. per minute (corrected). The calcium was 9.0 mg. per 100 cc. The agglutination test for undulant fever was negative. The stools were guaiac negative. X-ray study of the chest showed a triangular area of density in the left lower lobe, with radiating streaks of increased density to the hilus.

On the third hospital day the patient received 5,500,000 killed typhoid organisms intravenously, which produced a shaking chill and a maximum temperature of 103.8°F. There was slight improvement of the eye symptoms, but he continued to feel weak and tired and ran a temperature between 101 and 103°F. His appetite was almost nil, and he occasionally vomited. The breathing became rapid. The anemia increased in severity. On the tenth hospital day the hemoglobin was 7.2 gm. per 100 cc., and the red-cell count 2,700,000. The nonprotein nitrogen was 78 mg., the serum albumin 3.57 gm., the globulin 1.98 gm., and the fasting blood sugar 135 mg. per 100 cc.; the van den Bergh

reaction was 0.5 mg. per 100 cc. direct and 0.6 mg. total. Sputum cultures showed an abundant growth of *Staph. albus* and alpha-hemolytic streptococci. The sputum was negative for tumor cells.

The patient became oliguric and then anuric. A few purpuric, indurated skin lesions appeared on the lower abdomen. Dyspnea increased in severity. He coughed up small amounts of blood repeatedly. The blood pressure remained low. On the thirteenth hospital day the nonprotein nitrogen was 113 mg. per 100 cc., and prothrombin time 24 seconds (control, 15 seconds). The bromsulfalein test showed 18 per cent retention of the dye; the sodium was 142.4 milliequiv., the chloride 95 milliequiv., and the carbon dioxide 18.1 milliequiv. per liter, and the uric acid 10.0 mg. per 100 cc.

Therapy included digitalis, morphine, atropine, oxygen, penicillin and streptomycin.

The patient died on the fourteenth hospital day.

Differential Diagnosis

Dr. Richard H. Freyberg*: This man was a dye worker. I am not too familiar with the health hazards that workers in this occupation might encounter, but his occupation should be kept in mind. I do not know what he did at his "dye work" — how closely he may have been exposed to toxic agents. He was hospitalized with a chief complaint referable to the eyes. However, the present illness began with rheumatic manifestations, — arthralgia, stiffness and limitation of joint motions, — but throughout the illness there was little evidence of inflammation of the joints. These rheumatic phenomena were largely irritative. If there was inflammation, it was low grade, producing no clinical signs in most of the affected joints. The variations in the rheumatic symptoms are what is expected with various types of rheumatic illness — improvement with warmth, worsening in adverse weather and seasonal conditions — so that no lead to diagnosis comes from them.

Various unidentified drugs were administered. That is the usual story and should always put one on guard that there might have been administered a drug that could influence adversely the future course of the illness and that could even provoke lethal changes.

After several months with rheumatic symptoms, the patient began to show signs of systemic disease — tiredness and anorexia — and soon began to complain of the eye symptoms that prompted him to enter the hospital. These ocular abnormalities were other local signs of disease in a person who had a systemic disease. When he was examined in the Out Patient Department he had inflammation of various structures of the eyes, leading to the diagnoses of iritis and keratitis. Apparently, all the laboratory studies then conducted were directed to elucidate the pathology and the etiology of the ocular disease. It is to be assumed that syphilis was not a likely cause — the blood Hinton test was negative. It is important to note that at that time x-ray examination of the chest was reported negative. A few days before entering the hospital he developed respiratory symptoms including a cough quite promptly productive of generous amounts of sputum. Systemic symptoms increased in severity — he tired easily, lost weight and then became hoarse, indicating laryngeal involvement.

I think it is important to note that fifteen years previously, at the age of thirty, this man had a serious chronic illness for two years, characterized by severe systemic symptoms with the chief or only localizing symptoms in the intestinal tract. X-ray films were normal; I wonder whether the technic and the knowledge of persons doing roentgenographic studies at that time would be comparable to what we have now. At any rate it was reported that no intrinsic lesions were found. This suggests that neoplasm was eliminated as a cause for his illness then. If the patient had a chronic infection at that time, it was not recognized.

In his last illness, the patient showed evidence of chronic disease — although he was well nourished, he was pale. It is stated that there were no skin lesions. That may be of significant diagnostic importance. If his illness were related to his occupation, he should have had a contact-type dermatitis from dye. If one of certain diseases to be mentioned later existed, he might have manifested cutaneous signs that could be quite characteristic and diagnostic.

The only rheumatic manifestations were slight joint swelling and stiffness on motion. The knee was the only joint described as containing an increased amount of synovial fluid. Joint x-ray films are not mentioned, nor is there a report of joint fluid studies. There were "nodules over the elbows." Nodules can be of various sorts; sometimes subcutaneous swellings are called nodules when in my opinion they should not be. I raise the question whether these were rheumatic nodules or whether they were swellings of other nature. It is not stated whether they overlay the olecranon process, or whether they were distal to it. These are important points. Any nodule found in a patient whose diagnosis is in doubt should, in my opinion, be removed and studied histologically and culturally. No mention is made of such studies, which could be diagnostic of the nature of the disease. The question arises whether these so-called "nodules," were subcutaneous nodules characteristic of rheumatic fever or rheumatoid arthritis, periarteritis nodosa or gouty tophi. All must be considered. Also, the possibility of a chronic granuloma due to a tuberculous infection must be considered.

*Associate professor of clinical medicine, Cornell University Medical College, New York City.

The abdominal and neurologic abnormalities should be noted. The blood pressure remained low throughout the illness even though findings indicative of urinary-tract disease and kidney failure eventuated and the latter probably caused death.

The laboratory reported one observation of the white-cell count showing slight elevation without predominance of eosinophils and without much increase in cells of lymphatic origin. There were many white blood cells and casts in the urine. No organisms were reported, but it is not stated whether an acid-fast stain of the sediment or whether culture or animal inoculation to identify the presence of tubercle bacilli was done. The erythrocyte sedimentation rate was quite high.

The patient was given foreign protein in the form of typhoid organisms to cause a fever, I presume, with the hope of benefiting the eye disease. That is a common form of treatment for some inflammations of the eyes. Although there was slight improvement in the eye symptoms, the patient's general condition from then on became worse until death occurred.

X-ray examination of the chest showed a triangular shadow at the base. The roentgenologist will discuss this finding.

Dr. Stanley M. Wyman: I believe the density at the left base can be seen poorly behind the heart and in all probability represents considerable collapse of the left lower lobe. There is very probably a small amount of fluid in the left pleural space. The heart itself is not grossly remarkable. The diaphragm is quite high on both sides, causing the heart to lie transversely in position.

Dr. Freyberg: Were there x-ray films of the joints?

Dr. Wyman: The films of the hands and wrists taken on the same day show minimal osteoporosis of the ends of the long bones without, however, gross changes of the joint spaces and without appreciable changes in the periarticular soft tissues.

Dr. Freyberg: There is no evident osteoporosis, no cartilage damage and no subchondral bone change.

The anemia worsened, and signs of renal insufficiency and finally renal failure developed. The sputum showed different types of organisms, including the hemolytic streptococcus, which could have contributed to the anemia. It is not stated whether a search was made for tubercle bacilli in the sputum. There was increasing dyspnea, cough and expectoration of blood. Some ulcerative lesion of the respiratory tract allowed bleeding. The blood pressure remained low, suggesting the possibility of adrenal disease. There was a slight decrease in the blood sodium and chloride values. The high blood uric acid, I think, should not be confusing and should not be considered indicative of the existence of gout; hyperuricemia was undoubtedly due to renal failure and the retention of nitrogenous waste, which, of course, includes uric acid.

It is difficult for me to see why digitalis was used. Other therapeutic agents mentioned seem quite reasonable.

To put this all together, this man of middle age, a dye worker, had severe systemic, chronic illness, several years before the last sickness, a long period of good health and then a systemic disease characterized chiefly by rheumatic manifestations and inflammation of the eyes and later by respiratory symptoms, renal involvement and anemia. The patient was ill eight months; the disease worsened, and he died.

In differential diagnosis one should consider the possibilities of tuberculous infection and the existence of an atypical primary rheumatic disease, such as rheumatoid arthritis. But what else could the illness have been? Chronic renal disease with exacerbation, the existence of a neoplasm later in his illness causing some of the preterminal events, a diffuse collagen (vascular) disease including lupus erythematosus, scleroderma, dermatomyositis and periarteritis nodosa, and the question of chronic toxicity in connection with his work or treatment employed should be considered. What are the points in favor of or against these various possibilities? In many respects tuberculous infection could very well explain all the illness. The question would immediately be raised about the rheumatic manifestations — tuberculous rheumatism is not countenanced favorably in this country, but there are cases in which active tuberculosis has existed and in which arthralgia and mild synovial and capsular inflammation are present, but never to a very important degree; there is no destruction of cartilage or bone — different from the usual rheumatoid arthritis. In such cases the rheumatic manifestations are a minor part of the patient's illness just as they were in this case. We have been told nothing about a tuberculin test or a search for acid-fast bacilli.

Did this patient have a primary rheumatic disease? Symptoms of a rheumatic disease were not prominent for long, and I am not impressed with the possibility that this illness was primarily rheumatic. If rheumatoid arthritis were suspected, there should have been special studies, including biopsy of the nodules. Even if it existed in an atypical form, this did not cause his death. The findings are not characteristic of rheumatic fever or gout.

The episodes of renal disease could result from chronic nephritis although such episodes are not characteristic. Renal function was good for a short while at the beginning of the hospital stay, and there was never hypertension. The urinary signs

indicated pyelonephritis, the etiology of which we do not know from the protocol.

The existence of amyloidosis complicating an infectious or noninfectious inflammatory disease must be taken into consideration. Splenomegaly or hepatomegaly was not recognized on clinical examination. Some liver dysfunction existed as shown by the reduction of proteins and mild bromsulfalein retention. Congo-red test or biopsy to identify amyloid disease is not mentioned. With amyloidosis it would be uncommon to have pulmonary disease as prominent as this patient had. Neoplasm of the lung could be a late development and could cause many of the terminal findings, but there is no evidence of neoplasm shown by studies of the sputum, and the x-ray film is not definite.

Very serious consideration should be given to the possibility of the existence of one of the diffuse collagen (vascular) diseases. There were no signs of scleroderma. Neurodermatomyositis usually causes a great deal more pain. Periarteritis nodosa may be more or less painful, and I think it is a condition that could very well account for this patient's illness with pneumonitis, renal inflammation and rheumatic manifestations — all made exceedingly worse by typhoid injection.

Clinical Diagnosis

Undiagnosed systemic disease.

Dr. Freyberg's Diagnosis

? Tuberculosis, with pulmonary, ocular, renal and articular complications.

? Diffuse collagen (vascular) disease — such as periarteritis nodosa.

Anatomical Diagnoses

Subacute glomerulonephritis.

Periarteritis nodosa involving spleen and small bowel.

Myocarditis, acute, interstitial.

Pericarditis and pleuritis, fibrinopurulent.

Bronchopneumonia, severe, bilateral.

Pulmonary emboli, multiple, small.

Pulmonary infarction, recent, incomplete.

Femoral-vein thrombosis, left.

Pathological Discussion

Dr. Tracy B. Mallory: I am quite sure that the opinion of the medical service was confused, since the death certificate came to us as undiagnosed systemic disease.

The autopsy showed a severe fibrinopurulent pericarditis and pleuritis, a very strange looking heart with grayish and hemorrhagic foci scattered throughout the myocardium and endocardium in a most irregular pattern but with entirely normal heart valves. The liver was somewhat enlarged but not otherwise striking in appearance. The spleen was only slightly enlarged. The intestines showed several spots of hemorrhage on the mesenteric border. The kidneys were greatly swollen, weighing over 500 gm., and showed a marked mottling and numerous petechial hemorrhages on the surface. Numerous joints were opened, and all were grossly normal. The nodule from the elbow region was found with the aid of one of the clinicians who had felt it. The sum total of the gross findings was not very helpful in making any specific diagnosis.

Microscopical examination showed a very extensive, severe myocarditis with involvement also of the ventricular endocardium. It was surprising that there were no thrombi or vegetations on the endocardial surface, in spite of the fact that the connective tissue immediately beneath the endothelium was markedly infiltrated with polymorphonuclear leukocytes. There was comparatively little necrosis of muscle fibers, and the myocarditis was essentially interstitial. The lungs showed one small area of infarction. There was very extensive and severe edema and terminal bronchopneumonia. In the spleen and in the intestines characteristic vascular lesions of the type seen in periarteritis nodosa were found. The kidneys showed a severe acute glomerulonephritis. We were not able, in spite of many sections, to find any vascular lesions in either the heart or the kidneys, so that a simple diagnosis of periarteritis nodosa does not adequately explain the picture. Although such lesions were present in two organs, there was extensive involvement of many other organs where no vascular lesions were present. The lesion from the elbow was peculiar, and the experts have disagreed regarding classification as a rheumatic nodule. There was fibrinoid necrosis and reaction about it, but no clear palisading, and it was certainly not a typical rheumatoid nodule.

For want of anything better, I would be inclined to consider this as a case of one of the collagen diseases that does not fit clearly into any of the variously described clinical syndromes. In my experience the existence of diffuse glomerulonephritis is unusual in these cases except sometimes in lupus erythematosus. The rest of the picture — the sex, the age and so forth — would be much against a primary diagnosis of lupus erythematosus.

It is of interest that this is the third case within a very short period in which we have seen polyserositis and acute glomerulonephritis with associated dermatitis and scleritis. In one of them very widespread periarterial lesions were present, involving almost all organs. In another only two or three vessels were found after prolonged search. In the case under discussion there were several well marked lesions in two organs but not in the others.

A Physician: Is it unusual to find acute nephritis in the absence of red blood cells?

DR. MALLORY: In the terminal stages some red blood cells were eventually found although the nephritic lesions obviously had been going on for many weeks before death. It was a subacute rather than an acute lesion.

DR. ARTHUR S. PIER, JR.: Were the adrenal glands normal?

DR. MALLORY: Yes — in fact they did not even show as much lipoid depletion as one would see in almost any infectious disease.

DR. PIER: The low blood pressure was probably due to myocarditis?

DR. MALLORY: Yes.

CASE 36142

PRESENTATION OF CASE

A sixty-four-year-old housewife was admitted to the hospital because of difficulty in swallowing. The difficulty began three months before admission, when the patient thought she swallowed a chicken bone. A physician told her that her throat was inflamed and gave her a gargle to use. The dysphagia persisted, and a second physician noted a swelling in the neck. A basal metabolic rate was + 18 per cent. Later, only liquids could be swallowed, and she lost 22 pounds in the six weeks before admission. There was no hoarseness, no difficulty in breathing and no pain.

Physical examination revealed a nontender, rubbery mass, 5 by 6 cm., on the right lateral aspect of the thyroid cartilage, and a 3-cm. by 4-cm. mass of the same consistence on the left side of the thyroid gland. No lymph nodes were palpable. Laryngoscopic examination revealed bulging of the right hypopharyngeal wall. The heart and lungs were normal.

The pulse was 100, and the blood pressure 176 systolic, 100 diastolic.

The urine gave a ++ test for sugar, and the sediment contained many pus cells. Examination of the blood disclosed a red-cell count of 4,400,000, with a hemoglobin of 14.8 gm., and a white-cell count of 10,200, with 68 per cent neutrophils. An x-ray film showed a large mass on the right side of the neck, pushing the trachea and esophagus to the left. The chest was clear.

On the second hospital day, the patient became dyspneic, and a tracheotomy was performed. Tissue removed from the isthmus of the thyroid gland was reported as showing chronic thyroiditis. Her condition was satisfactory until the seventh hospital day, when she developed nausea, vomiting and diarrhea. On the following day she suddenly became unconscious, cyanotic, cold and sweating. In five minutes she regained consciousness. Physical examination following this showed a blood pressure of 100 systolic, 70 diastolic, and a pulse rate of 128. The deep reflexes were more active on the left, and positive Hoffmann and Babinski signs were elicited on that side. The pulse and respirations remained elevated, 108 and 35, respectively. On the following day, an x-ray film of the chest showed a small pneumothorax on the right. She improved for two days and then suddenly, on the twelfth hospital day, she became very dyspneic. Sixteen hundred cubic centimeters of air was removed from the right chest, and it was ascertained that she had no positive pressure in the pleural cavity. Despite further efforts to revive her, she died a short time later.

DIFFERENTIAL DIAGNOSIS

DR. OLIVER COPE: The first thing we hear about is the chicken bone. That immediately brings up the question, What relation had it to the mass in the right side of the neck? I think we had better discuss it before we see the x-ray films or the clinical chart. Obviously, this woman had a mass in the right side of the neck and some evidence that it extended to the left. The mass may have been an abscess, the result of chicken-bone perforation. In favor of that is the fact that when she arrived at the hospital she had no hoarseness. If the mass had been a thyroiditis or carcinoma arising in the region of the thyroid cartilage, it would have been likely to involve and paralyze the right recurrent laryngeal nerve. Later, the laryngologic examination revealed only the bulging; there is no comment about the vocal cords. I take it that they seemed to move equally and well. There is the possibility of sepsis. The thyroiditis recorded as the diagnosis of the biopsy specimen might have been secondary to the sepsis.

Could this patient have had a malignant process in the thyroid gland itself or arising in the region of the thyroid gland, pharynx or trachea? If it is cancer, it is sometimes hard to tell where it may have originated. One gets carcinoma in the esophagus invading the region of the thyroid gland, or invasion of the trachea from a cancer of the larynx, which might not have been picked up on laryngoscopic examination. I do not want to dismiss thyroid cancer. It is also possible, when the pathologist reported thyroiditis, that he confused it with a round-cell carcinoma of the thyroid gland. This confusion is by no means rare. It is a difficult differential point and the Pathology Department has occasionally had to reverse itself; a condition originally reported as Hashimoto type of thyroiditis, subsequently has turned out to be a round-cell carcinoma. I imagine it would be easy for the situation to be encountered in reverse.

Sepsis, acute thyroiditis or carcinoma in that region can give rise to respiratory obstruction. I think it is obvious that acute respiratory obstruction occasioned the tracheotomy. The reason for the operation presumably was not paralysis of the vocal cord so much as acute edema of the larynx. The

edema would have been due to increased venous and lymphatic pressures.

The urine gave a ++ test for sugar. I do not know what that means. It might be interpreted as being in favor of infection.

Coming down to the episode of loss of consciousness, the patient's condition was satisfactory until the seventeenth hospital day, when she developed nausea, vomiting and diarrhea. This loss of consciousness might be variously interpreted. First of all, it could have been a carotid-sinus reflex in a patient with a hypersensitive carotid sinus. One can have syncope from pressure on the sinus from a unilateral carcinomatous mass. That is a distinct possibility. On the other hand, following the episode the deep reflexes were found to be more active on the left side, which suggests a cerebral accident, perhaps arising from carotid-artery obstruction. A lesion on the right side of the neck might so have impaired the flow of blood in the carotid artery as to have given rise to cerebral anoxia with or without arterial thrombosis. She had hypertension, so that she might also have had a cerebral accident not specifically related to the mass in the neck. She also could have lost consciousness because of metastatic abscess or tumor. In anyone who has an abscess in the neck, or possibly a tumor, such sources of cerebral injury must be considered. I cannot solve the loss of consciousness and reflex changes in more definite detail. It does not seem to me that the loss of consciousness clarifies the origin of the neck mass.

The third accident that led to her death is described here as a pneumothorax. On the day following the cerebral episode studies showed a small pneumothorax on the right side. She improved for two days and then suddenly on the twenty-first hospital day became dyspneic, and 1600 cc. of air was removed and no evidence of pressure in the pleural cavity was noted. That is a peculiar circumstance. How did the pneumothorax come about? It is possible, though it seems to me unlikely, that the source of the air was the tracheotomy. The right pleural cavity and the line of reflection of the pleura rises high, close to the trachea. On the other hand, the tracheotomy was performed several days previously. It is also possible, but unlikely, that the patient had an infectious, gas-producing mediastinitis. The sepsis could have descended from the neck, perhaps from the tracheotomy wound, leading to mediastinitis and pneumothorax. On the other hand, she had had respiratory obstruction, and it is possible that an emphysematous bleb in the lung was ruptured during the expiratory phase of respiration, this break in the lung leading to the pneumothorax. The evidence is not sufficient for me to come any nearer the origin of the pneumothorax. The primary lesion may have been sepsis, thyroiditis of the Hashimoto type, or a tumor arising in the region of the thyroid gland.

May we see the x-ray films?

DR. JAMES J. MCCORT: These films were taken shortly after admission and show a large, soft-tissue tumor on the right side of the neck. The tumor is displacing both the trachea and the esophagus to the left. As one can see in the lateral film, the trachea and esophagus are also displaced slightly forward, indicating something between the esophagus and the spine. When the patient swallowed barium, only a small amount trickled into the esophagus. I believe this is the esophagus in here; it is hard to see any disturbance in the mucosal pattern, but I cannot see it well. Also there is no definite disturbance of the pattern of the trachea.

DR. COPE: Does it not look narrowed by pressure from outside?

DR. MCCORT: That is what it looks like. When the patient swallowed the barium, only a small amount went into the esophagus, the rest spilling into the trachea. This barium here is in the trachea.

DR. COPE: Is not the physical examination right? There is a mass on the left side.

DR. MCCORT: Yes, there is a small mass.

DR. COPE: That is not written into the x-ray interpretation, but it suggests that the physical examination was correct — it was a soft, rubbery mass. May we see the films of the chest?

DR. MCCORT: The films showing the pneumothorax are not available; we have only those taken at the time of admission. In both apexes there is increased density, which I take to be fibrosis. Here again we see displacement of the trachea. I do not see the chicken bone.

DR. COPE: I wonder if this could be it up here.

DR. MCCORT: No, I think that is an artifact. On the latest films there is no evidence of mediastinitis.

DR. COPE: No evidence of widening of the superior mediastinum?

DR. MCCORT: No, I can see no evidence.

DR. COPE: There is no evidence of the descent of this mass into the mediastinum?

DR. MCCORT: There is no evidence of that.

DR. COPE: I suppose it is not fair to put Dr. McCort on the spot too far. I would like to ask him later, after I have made my diagnosis, what diagnosis he would make on these films. I am really interested to know whether the X-Ray Department could spot this process as infection, as abscess or as a tumor mass.

May I see the clinical chart?

DR. TRACY B. MALLORY: Yes.

DR. COPE: There was a fever. The temperature on the initial days averaged 101°F. by rectum, and in the last days the temperature averaged 100°F. Was the patient receiving chemotherapy?

DR. MALLORY: Yes, she received penicillin throughout; the dosage started at 150,000 units and gradually increased to 800,000 units per day.

DR. COPE: The interpretation of the clinical chart is made difficult by the chemotherapy. My last question was a leading question. I would have to assume that this patient's chicken bone was of some importance. The sequence of events, including the complications (without paralysis of the vocal cord), spells an abscess rather than tumor or uncomplicated or specific type of thyroiditis. One can be wrong, because a tumor in the upper esophagus or hypopharynx can rapidly lead to infection, and the chicken bone might be a red herring. One might have a retroesophageal abscess, and yet the primary origin of it might be a tumor of the esophagus. I would interpret these films as showing a large retroesophageal abscess leading to respiratory obstruction on the basis of edema rather than paralysis of the vocal cord. The cerebral symptoms may, as I have said, have been due in part to carotid-sinus reflex or to a metastatic focus in the brain, a metastatic abscess, or they may have been due to a vascular accident in an older woman with hypertension.

About the final outcome, I suspect that the patient had mediastinitis and that the abscess will be found to have descended into the thorax. I am not sure how the air got there, but I think the story is in favor of abscess rather than tumor. Perhaps Dr. McCort knows the answer, but I would like to ask him what his diagnosis would be on the basis of the x-ray studies?

DR. MCCORT: The films were first seen by Dr. A. S. MacMillan in the Eye and Ear Infirmary, and he interpreted the mass, I believe, as tumor, extrinsic to the esophagus and trachea.

DR. COPE: That is interesting because the absence of lymph nodes puzzles me very much. I did not dwell on that; but if it was a tumor, it was a rapidly progressing round-cell type originating in the thyroid gland, and certainly I would have assumed that there would be widespread lymphatic involvement. When such a tumor has progressed to the extent of involving both lobes of the thyroid gland, lymph-node invasion is the rule. It may be that there was enough edema so that the lymph nodes were not separately palpable. In making my diagnosis I leaned heavily on the absence of lymph-node invasion. If one accepts the statement that there were no lymph nodes, a tumor is less likely.

DR. MCCORT: Dr. MacMillan's opinion in this case was that the long interval between the swallowing of the chicken bone and the development of an abscess was highly against it.

DR. COPE: There again the absence of paralysis of the vocal cord is against tumor. When one has a massive tumor leading to respiratory obstruction, cord paralysis would be expected. I interpreted that as being in favor of an abscess.

DR. MCCORT: If this was abscess, would you not expect it to spread into the pharynx?

DR. COPE: Not necessarily.

DR. MCCORT: It is on both sides of the neck and fairly well localized to the neck.

DR. COPE: That is a good point. Perhaps I should pay more attention to thyroiditis itself.

In the Hashimoto type of thyroiditis, there is involvement of the lymphoid apparatus, a lymph-node hyperplasia that extends far beyond the thyroid gland itself. The lymph nodes are often palpable though not greatly enlarged, and ordinarily there is no cord paralysis. I cannot read thyroiditis into the record.

DR. WYMAN RICHARDSON: If one looked at a well stained blood smear, one could tell whether sepsis was present, and that would help immensely.

DR. COPE: I did not see this patient clinically and am not responsible for the clinical report. Can

you interpret the record one way or the other?

Dr. Richardson: No; it is just a little against sepsis.

Clinical Diagnoses

Carcinoma of thyroid gland, with metastases.

Cerebral thrombosis.

Pneumothorax.

Dr. Cope's Diagnosis

Abscess of neck, with laryngeal edema and mediastinitis.

Anatomical Diagnoses

Malignant lymphoma, stem-cell type, involving hypopharynx, larynx, and esophagus and surrounding right thyroid gland.

Pulmonary embolism, acute, massive.

Pathological Discussion

Dr. Mallory: At autopsy we found a tumor mass involving the upper pole of the thyroid gland on the right side, the larynx and the esophagus. The major part of the tumor encircled the esophagus and the pharynx. The lymph nodes throughout the neck were normal in size, and none of them contained tumor. The tumor consisted of round cells that in any other location I would have diagnosed as a stem-cell lymphoma without hesitation. In the region of the thyroid gland one always wonders about that, since round-cell carcinomas of the gland do exist and are sometimes impossible to differentiate from lymphoma. My impression, however, is very strong in this case that this tumor was primarily in the esophageal wall rather than in the thyroid gland and involved the gland secondarily. The thyroid gland itself was somewhat enlarged, but its prominence was chiefly due to the fact that it was pushed forward by tumor. All the thyroid gland, as well as the isthmus, which was biopsied at the time of tracheotomy, showed severe chronic thyroiditis, quite different in character from the tumor, and I think there can be no question of any error in diagnosis.

There were some other findings of interest that were not foreshadowed in the clinical history. We found very little pneumothorax at the time of autopsy, and the immediate cause of death was a massive pulmonary embolus, which involved both major pulmonary arteries. There were also small vegetations on the mitral valve, the type described as marantic vegetations, seen not infrequently in patients in the terminal stages of cancer. We have on a few occasions seen emboli arise from these. This patient had several emboli to the spleen that produced infarction there.

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FRONTIERS OF KNOWLEDGE

AT HARVARD, the university professor has been given charge of the university laboratory with a select group of investigators, fellows, tutors, students and technicians. The University Laboratory of Physical Chemistry Related to Medicine and Public Health, under the direction of Edwin J. Cohn, unconfined by the usual boundaries of special sciences, will be devoted to the study of the constituents of body fluids and tissues and will focus its research upon the physical chemistry of proteins and other biologic substances that are characteristic of all living matter. Associate Professors John T. Edsall and John L. Oncley and Assistant Professor Walter L. Hughes, Jr., with fifteen colleagues, a number of graduate students and the necessary technicians, will be engaged in this work.

Not only are Dr. Cohn and his co-workers responsible for the extraction and concentration of the active principle in liver, effective in pernicious anemia, but also, because of this group's work, much of the blood involved in World War II was not spilled. Indeed, until the advent of the atomic bomb, hygiene and medical care had significantly reduced the efficiency of fire power as a method of mass slaughter. Surviving casualties and prisoners, in fact, were impeding the normal progress of war.

Who knows? Possibly among the vital enzyme systems or in the intimate structure of the protein molecule will be found, if not the defense against, at least the ameliorization of the H bomb's lethal ray.

The protein molecule, the element essential to life, is characterized by dissymmetry and great molecular weight. The late Lecomte du Noüy,* on the basis of mathematical probability, estimated that the chance formation out of inanimate matter of even the simplest imaginable protein is nil — that in any human sense it is impossible to account scientifically for all the phenomena pertaining to life. The promise of Wöhler's synthesis of urea a little over a hundred years ago, according to this distinguished French scientist, has not been borne out. There remains a hiatus in knowledge of the development of life from inorganic elements. To explain the origin of life and the development of man we must invoke what Eddington called "anti-chance."

In taking all scientific knowledge for their province it is not impious to hope that the Harvard scientists will be "thinking God's thoughts after Him." Pursuing their study of the origin of order from disorder as revealed in the body tissues and fluids of man they may find intimations that the anti-chance joker has been played many times. With an unlimited commission in choice of colleagues the workers in the University Laboratory might well invite a philosopher or a theologian or even a poet to sit in on their deliberations and brood with them on the characteristics of all living matter.

*du Noüy, L. *Human Destiny*. 289 pp. New York: Longmans, Green & Co., 1947.

A. M. A. DUES

THE fellows of the Massachusetts Medical Society received not long ago their bills for dues to the American Association for 1950, and presumably the rest of the members of the Association, countrywide, have received theirs, are receiving them or are about to receive them. The amendment to the by-laws of the American Medical Association whereby these dues are levied was explained in the *Journal* on January 12, 1950, in a letter from Dr. George F. Lull, secretary and general manager of the Association, so presumably the entire matter is familiar to all the *Journal's* readers.

In case there is still any misapprehension regarding the subject, however, the following information may be in order. An assessment of $25 was laid upon each member of the American Medical Association in 1949, to be collected through state or county societies, but since no penalty was attached to nonpayment, this assessment was voluntary. The assessment had nothing to do with the annual dues of the Massachusetts Medical Society for 1949 or 1950, or with the dues of the American Medical Association for 1950.

Prescribed dues of $25 are now being collected for the Association by state and county societies, and an active member who is delinquent in their payment for one year shall forfeit his membership as he might in any other organization of which he was a member. His membership in the Massachusetts Medical Society is not thereby placed in jeopardy.

Receipt of the bill for these dues has set off certain expected trigger mechanisms, although in a remarkably small number of members, who either pay, with indignation, or refuse to pay as a matter of principle, in a fixed belief, perhaps, that their Association can do no right. Fortunately, there are relatively few who carry their disagreement with their fellow physicians to this extreme.

Those who are still in doubt about the American Medical Association's achievements in the past and its constructive activities in the present should read again the letter from Dr. Louis Bauer, chairman of the Board of Trustees, which has recently been sent to every member of the Association.

GASTRIC PHOTOFLUOROGRAPHIC METHOD OF CANCER DETECTION

THE grim statistics of five-year survivals from gastric cancer with present methods of diagnosis and treatment (2 to 5 per cent), its prominence as a cause of death (30,000 to 40,000 in the United States as an estimate for 1949, or a third of all cancer deaths) and its annual incidence (15 to 46 per 100,000 total population or 1:900 persons over forty years of age) give impetus to a thorough investigation of all avenues of approach that may lead to earlier diagnosis and treatment. The five-year cure for resectable lesions is 25 per cent, and this figure is still higher in early lesions.

It is generally accepted that the conventional combined roentgenoscopic and roentgenographic technic, with use of the spot-film device, is the most efficient and accurate method of case finding.[1] Kirklin and Hodgson[2] point out that in a survey project of any magnitude this would take too much time and would be economically unsound. St. John, Swenson and Harvey,[3] with fluoroscopic examinations alone, uncovered 3 gastric cancers in 2500 examinations at the Presbyterian Hospital, New York City. A second approach has been tried by workers at the University of Minnesota Hospital[4-7] who have performed the customary radiologic study on the following groups selected as having precursors of gastric cancer: persons over fifty years of age with achlorhydria or hypochlorhydria; patients with pernicious anemia; patients with gastric polyps; patients with anemia; persons with occult blood in stools; patients with a family history of cancer; patients exhibiting atrophic gastritis by gastroscopy; and patients with gastric ulcer. The examinations were repeated at semiannual intervals. The yields from the patients with achlorhydria, gastric polyp and pernicious anemia were relatively high but admittedly represented a small segment of the total population. Furthermore, the cumbersome and uncomfortable procedures necessary to determine some of these groups would lose patient co-operation in large surveys.

The photofluorographic method of x-ray examination has proved of inestimable value in mass chest surveys for the armed forces. It is currently being

tested and evaluated by numerous civilian case-finding surveys throughout the country, and all evidence points to its continued value and expanded use.

The application of the Schmidt optical system, by the Danish engineer Helm, to the photofluorographic apparatus has made possible its use in gastrointestinal surveys.[8] The previous camera was relatively inefficient, particularly when applied to the thicker body parts, such as the abdomen, and the danger of excessive radiation exposure existed for both patient and operators. It required twenty times as much radiation per film of the stomach as is necessary for a standard radiograph. This would build up a not inconsiderable patient dose when one considers the possible re-examinations at six-month intervals in addition to immediate conventional examinations in suspicious cases. The Schmidt camera, by employing a large spherical mirror to reflect the light onto the film instead of the usual refractor type of lens, achieves an f/ number rating of 0.75. This results in a speed five times greater than the currently used photofluorographic camera without loss of detail, reducing the radiation hazard to within safe limits.

Roach, Sloan and Morgan[9] and Swenson[10] have begun pilot surveys with the gastric photofluorographic method. This consists of four to six views of the stomach taken by a technician after the patient has ingested the usual barium meal. The resulting films are studied by a panel of radiologists. Roach et al. are studying all male outpatients over forty years of age, a mixture of symptomatic and asymptomatic cases, with a conventional roentgenoscopic and roentgenographic restudy of all cases with abnormal photofluorograms. A second group of 1000 asymptomatic subjects is to be examined at six-month intervals over a five-year period to obtain an estimate of how frequently repeat photofluorographic studies would be of value. In the first 4000 cases examined by this group at Johns Hopkins Hospital, the following patient reaction, as yet unpublished, but quoted by Hilleboe,[11] occurred: "Out of 27 cases of gastric carcinoma detected by photofluorographic methods and confirmed by standard roentgenographic procedures, 8 cases had either no symptoms or such mild symptoms that it has not been possible to persuade these patients to undergo operation." Yet these are the ones sought after for early operation.

The appraisal of this method by most authors is one of caution and is best expounded by Morgan and his group:

> It must be stated at this time that no preconceived notions regarding the place of photofluorography in the cancer problem are held. The study has been undertaken to determine the reliability of the photofluorographic process in the detection of gastric malignancy, a process that has been virtually untried until the present time. The study will be pursued for a period of five years.

Actually, the true test of the efficacy of this procedure will result from the accrual of survival data from patients whose diagnoses have been confirmed at operation. These data, which it will take several years to obtain, will then have to be compared with present statistics before the final answer can be given.

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MAN AND HIS ENVIRONMENT

When Professor Douglas H. K. Lee returns from his present travels in India and the Near East to deliver the Cutter Lecture on Preventive Medicine under the auspices of the Harvard School of Public Health on April 24, those attending will hear a scientist with qualifications that are out of the ordinary. A professor of physiologic climatology in a school of geography and a lecturer in physiologic hygiene at the Johns Hopkins University School of Public Health and Hygiene, he could be characterized more concisely as an ecologist. His subject,

"Physiology as a Guide to Combating Tropical Stress," is certainly a part of human ecology, for tropical stress is hardly a simple chapter about tropical temperatures. Tropical stress results as much from a sociologic and biologic environment as from rain, sunshine and altitude. It is an effect of density and kinds of population, economics, agriculture and housing, and of insects, parasites, protozoa and their animal hosts. As defined in the catalogue of the Harvard School of Public Health, which has made human ecology a required course along with epidemiology and biostatistics, the subject combines "that branch of biology concerned with the relation between man and his environment and that branch of sociology dealing with the relations of people and institutions and their interdependency."

Physicians who glance at the invitation to hear Professor Lee lecture and decide that, since they are neither physiologists nor students of tropical hygiene, the banquet is not set for them are urged to reconsider. The physiologic mechanisms utilized to combat tropical stress are the same mechanisms of homeostasis that are combating the stresses of the temperate climate here in New England. They are serving the ends of men as far north as the Pole itself. Even at the Equator, tropical stress merges imperceptibly in temperate stress as the voyager ascends into the Andes, and abruptly should he choose to continue his journey by airplane.

In the kindergarten where man now finds himself, ecology is a new primer, which, with its companion, geography, forms a two-volume set entitled "One World, its Form and Function." Since modern communication has now shrunk that world to Lilliputian dimensions, it should be of more than passing interest to many to be able to hear someone who not only has opened the covers but also is busy cutting some of the pages of the two-volume set. The time comes all too soon when man, bored with his lessons, throws away all his books and, armed with his ignorance, his beliefs, his prejudices and his increasingly sharp sword, sets out to conquer all his global enemies in a single battle.

There is a kind of medical testimony that is weakened by efforts to give it strength: those who venture beyond what is requisite, by advancing hypotheses, instead of simply keeping close to the lines drawn by nature and fact, add nothing to the credit of the profession, and do not conform to what is required by modern medical jurisprudence.

Boston M. & S. J., *April 3, 1850*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

DUTTON — Richard Dutton, M.D., of Wakefield, died on March 10. He was in his seventy-fifth year.

Dr. Dutton received his degree from Harvard Medical School in 1901. He was formerly treasurer of Middlesex East District Medical Society and a councilor of the Massachusetts Medical Society, and he was a fellow of the American Medical Association.

His widow, two sons, a sister and a brother survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

PURIFICATION OF DIPHTHERIA TOXOID

All diphtheria toxoid produced in the future by the Division of Biologic Laboratories of the Massachusetts Department of Public Health will be purified. At present purified diphtheria toxoid is available in sufficient quantities to be used for the immunization of adults. It has been shown that toxoid treated to remove unwanted proteins causes much less reaction but retains its power to immunize.[1] Studies carried out in Fort Knox, Kentucky,[2] in which the Division of Biologic Laboratories participated, showed definite reduction of reaction in adults when purified toxoid was used. This study also showed the very great importance of Schick tests on adults before administration of toxoid, since it was found that persons with positive Schick reactions who needed the toxoid had comparatively little reaction but severe reactions occurred in the pseudoreactors, who did not need additional immunization. If Schick tests are not performed prior to immunization these people may suffer unnecessary and often severe reactions from injections that they do not need. This is true even though the toxoid is of the highest purity.

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GEORGE RICHARDS MINOT

(1885-1950)

It could not have been very long after George Richards Minot was born in 1885 before he was taken down Boston Harbor to see Minot's Ledge Lighthouse and learned it was there to save life. It bore the name of his great, great, great, great uncle. Anyone who knew his father, Dr. James Jackson Minot (1853-1938), can be sure the significance of the occasion was not overlooked. Love of the sea was ingrained in George Minot, and throughout all subsequent years vacations were spent on it or near it.

The part his family played in American medicine constantly surrounded him. A doctor's office and home were then customarily under the same roof, and the son could not help noticing his father's gentle ways with patients and his way of teaching students at the bedside rather than in the amphitheater. His great uncle, Dr. Francis Minot (1821-1899), had been professor of the theory and practice of physic at Harvard Medical School, his father's cousin, Dr. Charles Sedgwick Minot (1852-1914), was professor of histology and human embryology and his grandmother was the daughter of James Jackson.

After Harvard College came the Harvard Medical School, his family's school, from which he graduated in 1912, and then the Massachusetts General Hospital, his family's hospital. In 1913 came a tour of duty at Johns Hopkins under Dr. Thayer and Dr. Howell, and in 1915, already proficient in knowledge of the blood, he returned to Boston to enter on his life's work.

In 1921 he joined the editorial staff of the *Boston Medical and Surgical Journal*, later the *New England Journal of Medicine*, and remained with it until 1943.

In 1921 also a staggering blow was received: on October 15 glycosuria was discovered. Depending on a meticulous diet alone, however (C70, P80, F130 gm.), which controlled his diabetes, he lost but 5 pounds in sixteen months until, early in 1923, he was one of the first to take insulin. Perhaps after all, this tragedy in his life contributed to his later discovery. But he never could have carried on without the support he received from his wife who for twenty-eight years softened the blow. It was she who protected every minute of his existence, his going out and his coming in. It was she who weighed his food and saved him from the worry of the management of his disease, and she did it all in so unobtrusive a manner that neither he nor others realized it.

Between 1915 and 1925 he continued his studies of the blood, particularly of pernicious anemia, constantly traveling over the country exchanging information. Undoubtedly his own diet made it easier for him to appreciate Dr. George H. Whipple's work and gave him courage to feed liver in large quantities to patients with Addisonian anemia. He was most fortunate to have Dr. William P. Murphy to help him with the observations. In 1926 their studies were reported at a meeting of the Association of American Physicians, two years before Dr. Minot became professor of medicine at Harvard and director of the Thorndike Memorial Laboratory at the Boston City Hospital.

Drs. Minot and Murphy were the first physicians to bring a Nobel Prize to New England, and with one exception the only American practicing physicians to receive such an award. Honors then came thick and fast. Degrees were conferred by Harvard, Edinburgh and London. Medals of unusual distinction followed in profusion from universities, organizations and societies from all over the world. Upon his sixtieth birthday a dinner was tendered him by his colleagues, and after the occasion a memorial number of original articles by his students was published in a symposium on hematology.*

Like the beacon in Boston Harbor, Dr. Minot's career will always chart a course for young doctors to follow.

E. P. J.

**George R. Minot Symposium on Hematology.* Edited by W. Dameshek and F. H. L. Taylor. 984 pp. New York: Grune & Stratton, 1949.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Fundamentals of Otolaryngology: A textbook of ear, nose and throat diseases. By Lawrence R. Boies, M.D., clinical professor of otolaryngology, and director, Division of Otolaryngology, University of Minnesota Medical School. 8°, cloth, 443 pp., with 184 illustrations. Philadelphia: W. B. Saunders Company, 1949. $6.50.

The textbook is based on a plan used for the teaching of undergraduate medical students. The text is divided into three parts: the ear, the nose and the throat. The lists of references appended to the chapters are confined primarily to the literature of recent years. Historical data have been omitted in this basic book. The material is well arranged, and the text well written in a concise manner. The type, printing and illustrations are excellent. The heavily coated paper is probably justified by the large number of illustrations but makes the volume rather heavy for its size.

A History of Oto-Laryngology. By R. Scott Stevenson, M.D., F.R.C.S. (Ed.), and Douglas Guthrie, M.D., F.R.C.S. (Ed.). 8°, cloth, 155 pp., with 52 illustrations. Baltimore: Williams and Wilkins Company, 1949. $5.00.

This short history is well written in an easy style and should prove useful as an introduction to the larger separate histories of otology and laryngology. The material is well organized, and the volume well published. There is an extensive bibliography. The printing was done in Great Britain. The plates are tipped into the text, permitting the use of a light-weight paper.

Length of Life: A study of the life table. By Louis I. Dublin, Ph.D., second vice-president and statistician, Alfred J. Lotka, D.Sc., and Mortimer Spiegelman, F.S.A., assistant statistician, Metropolitan Life Insurance Company. Revised edition. 8°, cloth, 379 pp., with 32 illustrations and 94 tables. New York: Ronald Press Company, 1949. $7.00.

This standard reference work was first published in 1936. Since then marked progress has been made in the health and longevity of the American people. Because of the great amount of new material the book, in this revised edition, has been virtually rewritten, and chapters have been added on "Biological Factors Influencing Longevity and Mortality," including life hazards of the unborn and newborn child and the mother, and on "Forecast of Mortality and Longevity," dealing with a comparatively new field of importance in making estimates of future population. This chapter also includes an account of "generation" life tables. In the chapter entitled "Life Table Construction" a new short-cut method of computation is described. An appendix consists of life tables brought up to date. References to the pertinent literature are carried as footnotes throughout the text. The text is concluded with a list of sources of life tables.

There are indexes of names and subjects. The book is well published in every way. It is recommended for all medical and general libraries and should prove valuable, especially to public-health workers, actuaries and statisticians.

Fractures. By Paul B. Magnuson, M.D., professor of bone and joint surgery and chairman of the Department, Northwestern University Medical School, and attending surgeon, Passavant Memorial Hospital and Wesley Memorial Hospital, Chicago; and James K. Stack, M.D., assistant professor of bone and joint surgery, Northwestern University Medical School, and attending surgeon, Passavant Memorial Hospital and Cook County Hospital, Chicago. Fifth edition. 8°, cloth, 537 pp., with 323 illustrations. Philadelphia: J. B. Lippincott Company, 1949. $7.00.

The form and original objectives of this well known book have not been altered in the fifth edition. The material on the pathology of fractures has not been changed, and the emphasis continues to be placed on treatment. The chapter on compound fractures and the treatment of wounds has been brought up to date in the light of the experience gained in World War II, including the use of antibiotics, on the immediate closure of wounds and the use of full-thickness skin grafts to close defects immediately. There is a new chapter on the so-called "farmyard" reduction of fractures, presenting certain simple methods that can be used under almost all circumstances. The publishing is excellent in every way. The book should be in all medical libraries and in the libraries of surgeons interested in fractures.

Early Carcinoma of the Uterine Cervix: Pathogenesis and detection. By Hansjakob Wespi, M.D., chief, Obstetrical and Gynecological Department, Frauenfeld Hospital, Aarau, Switzerland. Translation by Marie Schiller, Ph.D. With a foreword and survey by Walter Schiller, M.D., pathologist of the Women and Children's Hospital, Chicago, and consultant pathologist, Cuneo Memorial Hospital and Columbus Hospital, Chicago. 8°, cloth, 271 pp., with 95 illustrations. New York: Grune and Stratton, 1949. $6.50.

This special monograph is based on the work of Dr. Wespi and his colleagues in the Gynecologic and Obstetric Department of the University of Zurich, beginning with 1937. Emphasis is placed on colposcopy, but the iodine test, the cytologic smear and other tests are discussed. There is an extensive bibliography. The plates are appended to the text, and therefore the use of a heavy-coated paper throughout is not justified. Otherwise the book is well published and should be in all collections on gynecology and cancer.

Stedman's Medical Dictionary. Edited by Norman B. Taylor, M.D., F.R.S.C., F.R.C.S. (Edin.), F.R.C.P. (Can.), M.R.C.S. (Lon.), University of Western Ontario. In collaboration with Allen E. Taylor, D.S.O., M.A. Seventeenth edition. 8°, cloth, 1361 pp., illustrated. Baltimore: Williams and Wilkins Company, 1949. With thumb index, $8.50; without thumb index, $8.00.

This standard medical dictionary has been revised to include new words and the elimination of obsolete terms. Trade names have been eliminated. Many definitions have been rewritten. A new feature is the inclusion of short biographic sketches of prominent persons in the history of medicine. The text is concluded with the new nomenclature in Latin and English adopted by the Anatomical Society of Great Britain and Ireland with the BNA equivalent. The dictionary is recommended for all medical and public libraries.

Clinical Neurology. By Bernard J. Alpers, M.D., Sc.D. (med.), professor of neurology, Jefferson Medical College of Philadelphia, and neurologist, Jefferson, Pennsylvania and Wills hospitals, Philadelphia. Second edition. 4°, cloth, 846 pp., with 240 illustrations. Philadelphia: F. A. Davis Company, 1949. $9.50.

This second edition of a standard work on neurology, first published in 1945, has been completely revised and brought up to date. The material on peripheral nerve injuries and cranial trauma has been revised in the light of the experience gained in World War II. The tables of differential diagnosis have been revised, and new illustrations have been included. The book is written primarily for the medical student and the general practitioner but should prove valuable to the neurologist. The text is printed in a two-column format. There is a comprehensive index and the publishing is excellent.

Electrotherapy and Light Therapy: With essentials of hydrotherapy and mechanotherapy. By Richard Kovács, M.D., professor of physical medicine, New York Polyclinic Medical School and Hospital, attending physical therapist, Manhattan State, Harlem Valley State and Columbus hospitals, visiting physical therapist, New York City Department of Correction Hospitals, consulting physical therapist, Mary Immaculate Hospital, Jamaica, New York, St. Charles Hospital, Port Jefferson, Long Island, Alexian Brothers Hospital, Elizabeth, New Jersey, area consultant, physical-medicine rehabilitation, Veterans Administration, and consultant in physical medicine, Office of the Surgeon General, Department

of the Army. Sixth edition. 8°, cloth, 739 pp., with 368 illustrations. Philadelphia: Lea and Febiger, 1949. $10.00.

This new edition of a standard work has been revised and brought up to date with the current advances in the subjects under consideration, including the experience gained from World War II. Material has been added to the chapter on electrophysics and electrodiagnosis. The chapter on low-frequency currents has been rewritten to include all the recent work on electric stimulation of muscle. New material has been included on microwave diathermy and ultrasound therapy. Also, a chapter on rehabilitation has been added. A large number of new illustrations have been included, and a number omitted. A glossary of terms concludes the text, and there is a good index. The publishing is excellent, and the book should be in all medical libraries and in the libraries of persons interested in physical medicine.

Human Pathology. By Howard T. Karsner, M.D., LL.D., medical-research adviser to the Bureau of Medicine and Surgery, United States Navy. Seventh edition. 4°, cloth, 927 pp., with 562 illustrations. Philadelphia: J. B. Lippincott Company, 1949. $12.00.

This standard text was first published in 1926, and the previous edition in 1942. This seventh edition has been thoroughly revised, and the material brought up to date. The chapter on the infectious diseases has been largely written and enlarged to include the diseases that came into prominence during World War II. The section on diseases of the liver has been entirely rewritten and rearranged in the light of extensive studies of recent years. Two chapters on diseases of the eye and of the skin have been added. Lists of references are appended to the various chapters. More than eight hundred references have been added to the bibliographies, and, to bring the lists within a reasonable scope, over nine hundred references have been deleted. Likewise, two hundred and forty-one illustrations have been added; one hundred and twenty-five have been deleted. There is a good index, and the publishing is excellent. The book should be in the reference collections of all medical libraries and available to all pathologists.

Obstetrics and Gynaecology: A synoptic guide to treatment. By Beatrice M. W. Dobbie, M.A., M.B., F.R.C.S., D.M.R.E. 8°, cloth, 358 pp., with 22 illustrations. New York: Paul B. Hoeber, Incorporated, 1949. $5.50.

This manual has been written primarily for the general practitioner and advanced students of medicine. The book deals almost exclusively with treatment and especially with preventive treatment. There is a differentiation between what a physician should do and what he should not do in a patient's home. The text was printed in Great Britain.

Iron Metabolism and Its Clinical Significance. By A. Vannotti, M.D., director of the Medical Polyclinic and professor of internal medicine, University of Lausanne; and A. Delachaux, M.D., lector of the Medical Polyclinic, University of Lausanne. Translated by Erwin Pulay, M.D. 8°, cloth, 267 pp., with 11 diagrams. New York: Grune and Stratton, 1949. $6.50.

The original German edition of this monograph was published in 1942 and embodies the original work of the authors on iron metabolism, carried out over a number of years. The material is divided into three parts: the biologic significance and normal metabolism of iron; iron metabolism under pathologic conditions; and clinical indications and practical considerations in iron therapy. The text is concluded with a bibliography and two indexes of subjects and authors. The printing was done in Great Britain.

NOTICES

BOSTON CHAPTER OF AMERICAN FEDERATION FOR CLINICAL RESEARCH

The April meeting of the Boston Chapter of the American Federation for Clinical Research will be held on the following dates:

Part I. Beth Israel Hospital, 8 p.m., April 10.

The Q-T Interval in Normal Children and in Rheumatic Fever. M. M. Alimurung, E. Craige, L. G. Joseph, E. F. Bland and B. F. Massell. (Children's Hospital and House of the Good Samaritan.)

The Effect of Exogenous Thyroid on Thyroid Function of Normal Human Subjects as Determined by Studies with Radioactive Iodine. M. A. Greer. (Evans Memorial Hospital.)

Acute Changes in Venous Tone by Pharmacologic Agents. J. Litter. (Evans Memorial Hospital.)

Blood Eosinophils Following Severe Gastrointestinal Hemorrhage. M. Zamcheck, H. S. Treager, G. J. Gabuzda, Jr. and R. C. Chalmers. (Boston City Hospital.)

The Pathogenesis of Pulmonary Edema in Mitral Stenosis. R. Gorlin, L. Dexter and J. W. Dow. (Peter Bent Brigham Hospital.)

Part II. Joseph H. Pratt Diagnostic Hospital, 8 p.m., April 17.

Effect of Atropine on Certain Gastric Functions in Patients with Duodenal Ulcer. B. F. Gill and J. S. Jessup. (Cushing Veterans Administration Hospital.)

The Measurement of Red-Cell Volume with Radioactive Chromium. K. Sterling and S. J. Gray. (Peter Bent Brigham Hospital.)

Studies of the Antidiuresis of Quiet Standing. A. S. Relman, F. H. Epstein, A. V. N. Goodyer and F. D. Lawrason. (Yale University School of Medicine and Evans Memorial Hospital.)

Hemodynamic and Renal-Function Effects of Venous Congestion of the Limbs in Patients with Diabetes Insipidus. W. E. Judson, F. H. Epstein, C. M. Tinsley, B. A. Burrows and R. W. Wilkins. (Evans Memorial Hospital.)

The Nephrotic Syndrome in Children: A physiologic interpretation based on clearance methods. J. Metcoff, W. Kelsey and C. A. Janeway. (Children's Medical Center.)

All interested physicians and medical students are cordially invited to attend.

GREATER BOSTON MEDICAL TECHNOLOGISTS ASSOCIATION

A meeting of the Greater Boston Medical Technologists Association will be held in the amphitheater of the Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston, on Tuesday, April 11, at 7:30 p.m. Dr. Sydney S. Gellis, associate in pediatrics, Harvard Medical School, chief, Medical Out-Patient Department, Children's Medical Center, and assistant physician-in-chief, Children's Medical Center, will speak on the subject "Homologous Serum Hepatitis: An occupational hazard to medical technologists?"

There will also be election of officers for the coming year, and delegates to the 1950 National Convention of Medical Technologists (ASCP) to be held in Houston, Texas, in June.

CUTTER LECTURE

The Cutter Lecture on Preventive Medicine, sponsored by the Harvard School of Public Health, will be given in the amphitheater of Building D, the Harvard Medical School, on April 24 at 5 p.m.

The lecturer will be Dr. Douglas H. K. Lee, professor of physiologic climatology in the Isaiah Bowman School of Geography, and lecturer in physiologic hygiene in the School of Public Health and Hygiene, both of Johns Hopkins University, Baltimore.

Dr. Lee, formerly professor of physiology at the University of Queensland, played an important part in developing the curriculum of the new School of Medicine at that institution. About three years ago he gave so impressive a series of seminars at the Johns Hopkins School of Hygiene that he was invited shortly after to accept his present post.

The medical profession and medical and public-health students and others interested are invited to attend.

MASSACHUSETTS PUBLIC HEALTH ASSOCIATION

The spring meeting of the Massachusetts Public Health Association will be held at the Hayden Auditorium, Boston University, 685 Commonwealth Avenue, Boston, on April 25. The theme of the meeting will be "Looking Ahead in Public Health."

Section meetings, which will include discussions on cerebral palsy, care of the aged, industrial health, sanitation, intercommunity reporting of diseases dangerous to the public health and group dynamics, will be held as usual from 3:30 to 5:30 p.m., followed by dinner at 6:00 p.m. The topic of the general evening session will be multiphasic screening.

Special events commemorating the sixtieth anniversary of the Association are also scheduled.

AMERICAN COLLEGE OF PHYSICIANS

The thirty-first annual meeting of the American College of Physicians will be held in Boston from April 17 to 21, with general headquarters in Mechanics Building, 111 Huntington Avenue, which will also be the site of general sessions, panel discussions and technical exhibits. The annual convocation and annual banquet will be held in the Grand Ballroom of the Hotel Statler.

Official registration will start on Monday morning, April 17, with advance registration of members and exhibitors on the preceding afternoon from 2:30 to 5:00. The registration bureau, located near the main entrance of Mechanics Building, will be open through the week from 8:30 a.m. to 5:45 p.m.

HARVARD SCHOOL OF PUBLIC HEALTH

A new course, entitled "Arthropod-Borne Diseases," will be given during April and May by Dr. H. S. Fuller, under the joint sponsorship of the departments of Tropical Public Health and Public Health Bacteriology of the Harvard School of Public Health. The object of this course is to provide the student with a satisfactory background in the field of arthropod-borne diseases. Particular attention is given to arthropods as *vectors* in the effort to integrate entomology with microbiology and with human disease. The course includes discussions of basic principles of morphology, physiology, behavior and ecology of arthropods as well as control measures. Emphasis is placed on the biologic relations among vector, pathogen and host.

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE AND RHODE ISLAND CHAPTER, AMERICAN PHYSICAL THERAPY ASSOCIATION

A combined meeting of the New England Society of Physical Medicine and the Rhode Island Chapter, American Physical Therapy Association, will be held at the Veterans Administration Hospital, Davis Park, Providence, Rhode Island, on Wednesday, April 19, at 7:30 p.m.

PROGRAM

7:30 p.m. Inspection of the Department of Physical Medicine.

8:00 p.m. Introductory Remarks. Frank Sullivan, M.D. manager, Veterans Administration Hospital.

Physical Treatment of Ultraviolet Light Allergy. Milos Lota, M.D., Rhode Island Hospital.

Method of Rapid, Progressive Neuromuscular Reeducation. A. W. Schenker, M.D., attending physiatrist, Halloran Veterans Administration Hospital, Staten Island, New York.

Physicians, physical therapists, occupational therapists, and correctional therapists are cordially invited to attend.

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 3–MAY 19. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 286, issue of August 18.

JANUARY 9–DECEMBER 1. Laboratory Courses at Communicable Disease Center, Atlanta, Georgia. Page 950, issue of December 8.

APRIL 10. Boston Chapter of American Federation for Clinical Research. Page 567.

APRIL 10 AND 11. American College of Surgeons. Page 427, issue of March 16.

APRIL 11. Greater Boston Medical Technologists Association. Page 567.

APRIL 13. The Value of the Bone Bank. Dr. Joseph H. Shortell, Pentucket Association of Physicians. 8:30 p.m. Haverhill.

APRIL 14 AND 15. American Academy of Neurology. Page 528, issue of March 30.

APRIL 15. Springfield Hospital. Page 488, issue of March 23.

APRIL 17. Boston Lying-in Hospital Obstetric Round Table. Page 888, issue of December 1.

APRIL 17. Hartford Medical Society. Page 386, issue of March 9.

APRIL 17. Boston Chapter of American Federation for Clinical Research. Page 567.

APRIL 17–21. American College of Physicians. Notice above.

APRIL 18. Springfield Hospital. Page 488, issue of March 23.

APRIL 19. Tufts Medical Alumni Association. Page 488, issue of March 23.

APRIL 19. New England Society of Physical Medicine and Rhode Island Chapter, American Physical Therapy Association. Notice above.

APRIL 21. National Rehabilitation Association. Page 488, issue of March 23.

APRIL 21. Sixtieth Anniversary of Clark University. Page 428, issue of March 16.

APRIL 22–29. American Association of Industrial Physicians and Surgeons. Page 305, issue of February 23.

APRIL 24. Cutter Lecture. Page 567.

APRIL 24–28. National Tuberculosis Association. Page 678, issue of October 27.

APRIL 25. Massachusetts Public Health Association. Notice above.

APRIL 25–28. Philadelphia County Medical Society. Page 386, issue of March 9.

APRIL 26. New England Obstetrical and Gynecological Society. Rhode Island Hospital and Providence Lying-in Hospital, Providence, Rhode Island.

APRIL 27. 94th Infantry Division Lecture. Page 528, issue of March 30.

APRIL 29. Eastern Section of American Congress of Physical Medicine. Page 305, issue of February 23.

APRIL 29. Long Island College of Medicine Alumni Day. Page 348, issue of March 2.

MAY 3. Norfolk District Medical Society Anniversary Dinner.

MAY 3–7. Second European Congress of National Associations of Gastroenterology. Page 428, issue of March 16.

MAY 4. Suffolk District Censors' Meeting. Page 234, issue of February 9.

MAY 8. New England Cardiovascular Society. Annual Meeting.

MAY 10. Massachusetts Society of Examining Physicians. Page 528, issue of March 30.

MAY 10. Massachusetts Chapter of American Academy of General Practice. Page 528, issue of March 30.

MAY 14–19. International and Fourth American Congress of Obstetrics and Gynecology. Page 160, issue of January 26.

MAY 16–18. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

MAY 17. Luncheon Meeting. Section on Diseases of the Eye, Ear, Nose and Throat, Massachusetts Medical Society. Hotel Statler, Boston, 12:00 m.

MAY 22 AND 23. National Research Council Committee on Human Reproduction. Page 488, issue of March 23.

MAY 24–26. American Association of Genito-Urinary Surgeons. Page 234, issue of February 9.

JUNE 22–25. American College of Chest Physicians. Page 270, issue of February 16.

JUNE 24 AND 25. American Society for the Study of Sterility. Page 38, issue of January 5.

JUNE 26–30. American Physicians Art Association. Page 428, issue of March 16.

JUNE 26–30. American Medical Association. Annual Session. San Francisco, California.

JULY 17–22. International Congress for Scientific Research. Page xvii, issue of September 1.

AUGUST 21–26. International Society of Hematology. Page 888, issue of December 1.

AUGUST 28–SEPTEMBER 1. American Congress of Physical Medicine. Page 428, issue of March 16.

AUGUST 31–SEPTEMBER 7. World Federation for Mental Health. Page 306, issue of February 23.

SEPTEMBER 3–9. International Heart Congress. Page 160, issue of January 26.

SEPTEMBER 27–29. Mississippi Valley Medical Society. Page 991, issue of December 15.

OCTOBER 12–14. American Association of Blood Banks. Page 428, issue of March 16.

NOVEMBER 1. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

DISTRICT MEDICAL SOCIETIES

NORFOLK

MAY 3. Anniversary Dinner.

SUFFOLK

MAY 4. Censors' Meeting.

(*Notices concluded on page xv*)